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IMPORTANCE OF BIOLOGICAL RESEARCH IN INDUSTRIAL MEDICINE

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• *The biological laboratory is a valuable partner of the practitioner of medicine. A myriad of new chemicals are becoming part of our everyday life. The intoxications to which they can give rise appear in both industrial and general practice.*

The most commonly used toxic substances can be classed as metals, halogenated hydrocarbons, aromatic hydrocarbons, gases, dusts, insecticides, and radioactive materials. A tabulation shows in detail how the appropriate biological tests help the physician to establish a diagnosis and to eliminate the cause.

The biological laboratory, in addition, carries out necessary research on the acute, subacute, and chronic effects of exposure to unfamiliar chemicals. Examples are given to illustrate the often unexpected phenomena encountered, such as the influence of particle size on the toxicity of various substances.

The general practitioner is frequently confronted with disease entities that are characteristic of those encountered in the general population but may be of occupational origin. Unfortunately, the differentiation of occupational diseases from those that are nonindustrial is a difficult clinical problem owing to the fact that the signs, symptoms, and physical findings resulting from industrial poisons so closely imitate commonly occurring illnesses. Fortunately there are available biological laboratory procedures that can be of invaluable assistance in arriving at a final diagnosis. The tests may be used to determine (*a*) specific toxic substances in biological specimens, (*b*) metabolic or conjugated products of the toxic agent, and (*c*) changes in normal constituents of body tissues and fluids. The findings of tests (*a*) and (*b*) are specific, whereas the findings of test (*c*) may be specific in some instances but in general are nonspecific.

The problem that confronts the general practitioner is not a simple one. If he considers all diseases as nonoccupational, there may be an unnecessary delay in final diagnosis and proper therapy. Conversely, there may be a tendency for some physicians to associate too many illnesses with occupations, again delaying proper diagnosis. If there is a question regarding diagnosis, the use of laboratory tests may provide the data needed in conjunction with a careful occupational and medical history to make a sound decision. Thus the biological laboratory becomes a valuable partner of the general practitioner. It can be anticipated that there will be greater dependence upon the laboratory in the future owing to the marked increase in potential contacts of the industrial worker and the general public with the myriad of new chemicals that are becoming a part of our everyday life. The table, which shows symptoms, signs, organs, or systems affected, and indicated biological tests relating to some commonly used toxic substances, presents some representative examples of tests that are currently available.

Functions of a Biological Research Laboratory

Most of the laboratory procedures listed in the table have originated in research laboratories. Because new substances or materials possessing potential health hazards are coming into use (for instance, insecticides and radioactive materials), continuing research is necessary. The foregoing may serve as an offhand explanation for the existence of biological laboratories in industrial medicine. But the functions of such a laboratory outlined in the accompanying diagram indicate a scope of activities that render this explanation quite inadequate.

Virtually all the functions of the laboratory may be considered research, in that new information is made available. However, the work of the laboratory falls into two categories: one consisting mainly of routine acute toxicity and range-finding tests and the other comprising more complex investigations dealing with the metabolism of toxic agents, mechanism of biological response, and organic and functional changes that require utilization of the most up-to-date research tools.

Types of Toxicologic Studies

A toxicologic study, to be complete, considers three phases: the acute, the subacute, and the chronic.

Acute Toxicity.—The immediate toxicity of a single exposure or dose is determined by administration through

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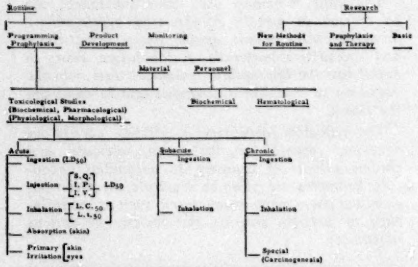
the various routes by which a substance can gain entrance into the body. These determinations will usually categorize the substance, since there is available in the literature a considerable storehouse of data on a wide variety of compounds with which the data on a new substance can be compared. A convenient measure of acute toxicity and standard of comparison is the LD_{50}, the dose that kills one-half of the animals and is expressed as milligrams per kilogram of body weight. Differences in the LD_{50} for the various routes are due to differences in rates of absorption, which allow for some detoxification and excretion. These differences give some indication of the pharmacological or biochemical behavior of the substance.

In a determination of toxicity by inhalation, a standard of comparison is the concentration of the gas or vapor that will kill one-half of the animals in a given time, the LC_{50}, or the Lt_{50}, the time required to kill one-half of the animals by a given concentration of a gas or vapor. Also, information on skin absorption, primary skin irritation, and irritation of the eyes can be obtained concurrently with that on acute toxicity.



Functions of a biological laboratory as a teammate in industrial hygiene. (S.Q., subcutaneous.)

Subacute Toxicity.—The subacute toxicity is represented by the reaction to multiple doses of sublethal magnitude, providing preliminary data on potential chronic effects in a relatively short period. This period is usually three to six months.

Chronic Toxicity.—In chronic toxicity, on the other hand, the study is designed to determine the subtler biochemical, physiological, and morphological changes. It is a long-term investigation generally requiring two or more years. Exposure levels may be purposely exaggerated but are sufficiently close to those likely to be encountered in the "field" or in public use to yield results simulating those that might be expected under the worst possible conditions of practical use. Chronic toxicity studies are exceedingly useful investigational procedures for another reason, since they afford an opportunity to study the mechanism by which a substance exerts its deleterious biological action and thus may provide a basis for early diagnosis of injury or a measure of excessive absorption before injury occurs.

Because diverse animal species may exhibit important differences in ability to absorb, metabolize, and excrete given substances, it is advisable to use more than one species in order to circumvent pitfalls owing to species peculiarities or anomalies. In studying chronic toxicity it is customary to use a homogeneous group of young animals of approximately the same age and weight. The chemical to be tested is mixed in a predetermined percentage with the food. The daily food intake, and hence the daily ingestion of the test chemical, is determined and recorded. Any deviation of the growth curve of the experimental group from that of an identical control group is a sensitive indication of toxicity.

The examination of blood and urine for the toxic agent or its metabolic products and the determination of biological changes of normal body constituents such as nonprotein nitrogen and enzymes may provide early indications of toxic action. Morphological examinations of the blood of the animals may reveal the presence of anemia or granulocytopenia. Quantitative analysis of aliquot portions of various organs will yield information on the distribution and storage of the ingested chemical throughout the body. Changes in weight of organs, as liver and kidneys, in relation to body weight provide another measure of early response. Various intracellular enzymes, such as ribonuclease, lipase, phosphatase, certain proteases, and others, may be visualized by newer histochemical techniques. The demonstrated diminution or absence of certain of the intracelluar enzymes could be evidence of functional cellular disturbance caused by the ingested chemical. The cumulative, deleterious effects of long-continued ingestion of a toxic chemical are often demonstrable at autopsy in gross or microscopic structural changes in one or more organs or tissues.

Pulmonary Response to Particulate Matter

Structural pulmonary changes resulting from the inhalation of various dusts, while not strictly speaking a "toxic" manifestation, are the reaction of pulmonary parenchyma to chronic irritation by the foreign material. The potential long-term pulmonary hazard of a respirable dust may be determined in two ways, and both are usually advisable: by intratracheal injection of aqueous suspensions and by inhalation-chamber technique. The former requires no specialized equipment provided the dust to be tested is available in the proper particle size. Generally a single maximal dose is injected, but there is no valid objection to the injection of multiple doses at spaced intervals. This technique quickly overwhelms the clearance mechanism of the lungs and brings about a rapid development of the lesions that, by the inhalation-chamber technique, would arise more slowly. The inhalation-chamber technique requires specially constructed equipment for producing the desired concentration of dust of the proper particle size.

Both techniques necessitate the use of comparable control groups parallel with the group receiving the experimental dust. A positive control group is exposed to quartz dust, which produces typical silicosis, while a negative control group is exposed to a dust generally considered harmless, such as limestone. The particle size and dust concentrations of the control dusts should also be comparable. The evolution of pulmonary lesions can be studied by killing of animals at spaced intervals. Portions of the lungs may be analyzed quantitatively for

Symptoms, Signs, Organs, or Systems Affected and Diagnostic Laboratory Tests Relating to Some Commonly Used Toxic Substances

Substance	Symptoms	Signs	Organ or System Affected	Indicated Biological Tests
		Metals		
Lead	Metallic taste Anorexia Weakness Weight loss Abdominal discomfort Constipation Pains in muscles and joints Irritability	Pallor Blue line on gums Muscle weakness Tremors Abdominal tenderness	Gastrointestinal Hemopoietic Nervous	Lead in blood or urine Porphyrins Blood cell counts, including stippled cells and reticulocytes
Mercury	Metallic taste Anorexia Salivation Sore gums Irritability Tremors Abdominal discomfort Insomnia	Stomatitis Gingivitis Fetid breath Tremors Erethism Dermatographia Pallor Psychic disturbances	Mucous membrane of oral cavity Gastrointestinal Nervous Renal	Urinalysis Mercury in urine Renal function
Chromium	Irritation of upper respiratory tract Ulcers of the skin	Characteristic skin ulcers Perforation of nasal septum Dermatitis Conjunctivitis	Skin Mucous membrane	(Environmental analyses)
Cadmium	Dryness and soreness of throat Metallic taste Cough Substernal pain Headache Dizziness Dyspnea	Pulmonary edema Tachycardia Tachypnea (Rales may not be noted until near death)	Respiratory	Blood cell count (leukocytosis, lymphocytosis)
		Halogenated Hydrocarbons		
Carbon tetrachloride	Headache Nausea Vomiting Anorexia Fatigue	Jaundice Edema of face and ankles Hepatomegaly Oliguria	Gastrointestinal Renal Hepatic	Routine urinalysis Liver function tests Renal function tests Blood nonprotein nitrogen Blood creatinine
Trichloroethylene	Dyspnea Headache Dizziness Disturbed gait Fatigue Anorexia Nausea Somnolence Numerous other subjective complaints	Tremors Abdominal tenderness Dermatitis Sluggish response to questions Diminished vision Cardiac arrhythmia (Objective physical findings scant)	Nervous Cardiac	Analysis of urine for trichloracetic acid
		Aromatic Hydrocarbons		
Benzol	Headache Dizziness Anorexia Insomnia Weakness Fatigue Muscle cramps	Purpura Bleeding from gums	Hemopoietic	Complete blood cell count (anemia, leukopenia) Urine sulfate ratio
Aniline	Headache Vertigo Weakness Unsteady gait	Cyanosis Weak pulse Muscular tremors Brown discoloration of urine	Blood	Methemoglobin Blood cell count
		Gases		
Carbon monoxide	Headache Dizziness Nausea Vomiting Blurred vision	Tachycardia Peripheral vasodilation Cherry-red color of mucous membranes Weak, thready pulse	Blood (asphyxial phenomenon)	Determination of carboxyhemoglobin
Hydrogen sulfide	Irritation of eyes and respiratory tract Photophobia Vertigo Headache	Reddened eyes Hyperpnea	Respiratory	(Environmental analysis for hydrogen sulfide)
Nitrogen dioxide	Cough Dyspnea Pains in chest	Pulmonary edema Peripheral vasodilation Respiratory paralysis Unconsciousness	Respiratory	Methemoglobin Chest x-ray
		Insecticides		
Chlorophenothane (DDT)	Muscle tremors Tonic and clonic convulsions Hyperexcitability Anorexia	Twitching of eyelids Tremors Muscular weakness	Hepatic Nervous	Blood cell count Analysis of urine for organic chlorides Liver function tests
Organic phosphorus compounds	Tachypnea Ataxia Tremors Anorexia Nausea Vomiting Blurring of vision	Lacrimation Slurring of speech Salivation Cyanosis Miosis Hypertension Tonic and clonic convulsions Hyperhidrosis	Nervous	Serum cholinesterase
		Dusts		
Silica	Dyspnea Cough Anorexia Fatigue	Cyanosis Reduction in vital capacity Clubbing of fingers	Respiratory-cardiac	X-ray

Symptoms, Signs, Organs, or Systems Affected and Diagnostic Laboratory Tests Relating to Some Commonly Used Toxic Substances—Continued

Substance	Symptoms	Signs	Organ or System Affected	Indicated Biological Tests
Silicates (feldspar, talc clay)	If present, similar to silica but much milder; may result from silica contamination	Generally very few—reduction in vital capacity in advanced cases only	Respiratory-cardiac	X-ray
Coal	As for silicates (above)			
		Radioactive Materials		
	Erythema Skin lesions Burns Malaise Nausea Vomiting Purpura	Capillary fragility Petechiae Ecchymoses Hematomas Ulcers of gastrointestinal tract Anemia Loss of hair Cataracts Neoplasia	Hematopoietic Reproductive	Complete blood cell counts (anemia, leukopenia, lymphopenia) Bone marrow studies Biopsy, ionization chamber

their content of the inhaled or injected dust. Sections of the lungs can be incinerated, and the distribution of the ash (inclusive of the inhaled dust) can then be determined in relation to the lesions.

Research on Halophosphors

A toxicologic study of several new formulations of halophosphors used in fluorescent tubes is illustrative of a typical problem. The phosphors were composed largely of materials commonly recognized to be biologically inert, but they also contained antimony trioxide, about which toxicologic information was fragmentary and inadequate. The purpose of the investigation was to evaluate the hazard, if any, of the halophosphors in their entireties and of the antimony component, in particular, to the plant personnel and to the consuming public. This investigation followed closely the pattern outlined. The results [1] provided basic information that indicated the degree of hazard that might be associated with handling the material and the type and extent of control measures needed. The report gave management the assurance that the products could be used without harm to the plant personnel or the consumer.

Carcinogenesis

The study of the carcinogenic potential of a substance is also not an investigation of "toxicity" but one of chronic irritation. The conventional technique consists of the repeated application, over a prolonged period, of the suspected material to the skin of susceptible mice. The tissue response may be one of hyperplasia, hyperkeratosis, papilloma formation, or the development of a frank carcinoma. The limitations of present techniques are well recognized. There is much need for research to develop additional procedures that will permit more meaningful appraisal of carcinogenicity.

Product Development

Participation in product development is another important function of the biological laboratory. Many compounds may be synthesized that represent more or less minor variations of a basically new structure. Toxicologic studies may serve to eliminate the more toxic ones, so that research activities can be directed toward the less toxic compounds. For this reason it is customary to utilize a skeletonized series of acute toxicity tests that can be completed in a relatively short time and in which a reduced number of animals is used. This technique, termed "range-finding," [2] has been useful for toxicologic classification of a large list of compounds.[3]

Basic Research

Basic research in industrial toxicology is just as essential as it is in any other field. Progress in toxicologic knowledge is dependent in a large measure on the new facts that come from such fundamental investigations. New and improved laboratory techniques enhance the quality and quantity of work. Newer information on the subtler functional changes provides a basis for earlier and more reliable diagnostic procedures, and hence better prophylactic and therapeutic measures can be made available. Such scientific progress is exemplified by better range-finding techniques, use of chelating agents in heavy metal poisoning, and treatment of nuclear radiation damage by certain serums or tissue extracts.

Some years ago, during a toxicologic investigation, rabbits were killed with but a few milligrams of a particular form of finely divided silica injected intravenously. Although death was recognized to be caused by pulmonary embolism (anaphylactoid phenomenon), the minuteness of the dose could not be reconciled with the extensive embolization necessary for a fatal outcome. Studies [4] showed that a few milligrams of finely divided particulate matter could adsorb up to nine times its weight of plasma protein and thereby be converted into rather bulky, sticky, aggregates. The mechanism of pulmonary embolism thus was no longer a mystery.

Another example of the problem involving the basic mechanism of occupational disease was encountered during the investigation of the previously mentioned halophosphors. When 10 mg. of an aqueous suspension of extremely fine (0.04μ) insoluble antimony trioxide was injected intratracheally into rats, fulminating death occurred regularly even though no casualties resulted with the intratracheal injection of 7.5 times this amount of the same material in a larger particle size. The mechanism of such deaths is not completely understood. Judging from the massive pulmonary edema that precedes and accompanies death, there is a hitherto undescribed, but basic, biological phenomenon involved. We believe that this phenomenon is probably caused by an explosive change of pulmonary capillary semipermeability to permeability, due to contact of capillary endothelium with an enormous number of extremely fine particles.

Comment

A generalization of the role that biological research plays in industrial medicine may be stated in algebraic terms. This generalization is based on the premise that industrial hygiene is basically concerned with a special case of the general equation:

$$X\ Man + Y\ Environment = Z\ Reaction$$

The initial objective is to evaluate the variables X and Y so that Z can be predicted. The ultimate goal is to control X and Y so that the value of Z approaches zero, and the effectiveness of the industrial hygiene team is measured by its ability to approximate this goal. The value of X can be defined in terms of present health and well-being based on a careful occupational and clinical history and a thorough preplacement physical examination. This scouting should embrace the psychic as well as the physical make-up of the worker. The value of Y can be defined in terms of the quality and quantity of the chemical or physical agent present in the environment. This value takes into account the potential organic and functional response to the agent based on past experience or on the results of laboratory investigation.

In the biological laboratory more precise values can be obtained by substituting homogeneous animal groups for heterogeneous man and by carefully controlling the environment. The type and magnitude of reaction, Z, is studied with all resources available (biochemical, pharmacological, physiological, and morphological) to arrive at a thorough understanding of the mechanism of the reaction and its quantitative relation to X and Y.

Conclusions

A brief review of the functions of a biological laboratory shows the significant contributions that can be made to industrial medicine. Such a laboratory not only supplies the basic information on which to build adequate engineering control but it also supplies the medical profession with knowledge that is essential for continuing progress in the diagnosis, treatment, and prevention of occupational diseases.

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A PHYSICIAN LOOKS AT ATHLETICS

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Differences of opinion among coaches and team physicians and a generalized lack of understanding and coordinated effort have, all too frequently, diminished the effectiveness of methods of prevention and treatment of athletic injuries. A clear definition of the separate duties and responsibilities of coach, physician, team manager, and school administrator and an awareness of the necessity for cooperation and integration among the team leaders is basic to any program aimed at reducing accidents during sports participation.

Coaches and school administrators often complain that team physicians lack a sincere interest in athletics. Consequently, they are too quick to disqualify players, they have little understanding of the special problems of athletic injuries, and they fail to be explicit when giving instructions to coach and players. Physicians so generally frown on organized athletics that coaches tend to heed the opinions of their trainers and assistants rather than those of the team doctors. This situation, prevalent in secondary school sports, is less marked in college athletics and rarer still in adult professional athletics. Numerous reforms in boxing, for example, resulted from the recommendations of physicians. Physicians sometimes feel that coaches are more concerned with the success of the team than with the health and safety of its members. Doctors, among others, wonder if overemphasis on sports will distort a player's sense of values. Then, too, the dangers inherent in rough sports such as football, boxing, lacrosse, soccer, and water polo are especially obvious to medical men.

• For effective prevention and treatment of athletic injuries there must be cooperation on the part of coaches, team managers, school administrators, and physicians. The team doctor has two main functions: he must prevent injuries whenever possible and treat them when they occur. He must examine each player before participation in an event and keep meticulous medical histories; he must cooperate with coaches and sponsors in the conditioning and uniforming of players; he must treat injuries and, if necessary, follow their course beyond the playing season; and he must be in attendance at all events where the injury hazard is pronounced.

Proper protection of the brain, the eyes, and the teeth requires special measures, with which the physician must be familiar. He must make sure that the protective equipment is worn. He must also supervise the conditioning program.

In football and in boxing, moving the head or neck of an injured participant may make the difference between a temporary and a permanent disability; first aid, and the subsequent transportation of the injured person, are responsibilities for the physician.

School administrators maintain outwardly cordial relations, of course, with coaches and team physicians. In secondary schools, the administrator's main concerns are to keep his school free of legal responsibilities for injuries sustained by players and to avoid involvement with the angry and confused parents of injured athletes.

Often, however, the administrator has failed to provide the proper protective equipment, safe playing fields, and protection from accident and illness that would enable him to achieve his objectives. Every school should have a formal, written code governing responsibility for athletic injuries that is known to all participants as well as to their parents, physicians, and school authorities.

The Team Physician

The team doctor has two main functions: he must prevent injury whenever possible and he must treat such injuries as do occur so that players achieve maximum physical restoration. The physician should be present at games, prepared to give immediate medical care when needed. Although the physician must conserve the playing strength of his team, his prime concern is maintenance of the health of his charges and the prevention of permanent disabilities. The team doctor should be responsible for (1) a meticulous medical history and physical examination of each player prior to his participation; (2) the conditioning and the proper uniforming of players, in cooperation with coaches and sponsors; (3) the treatment of athletic injuries, including, when necessary, follow-up beyond the playing season; and (4) attendance at all events where the injury hazard is pronounced.

When a history or clinical examination reveals evidence of nephritis, hypertension, heart murmur, tuberculosis, diabetes, blood dyscrasia, or peripheral vascular disease, all indicated modern laboratory procedures and electrical diagnostic adjuncts such as radiography, fluoroscopy, electrocardiography, and oscillometry must be utilized for accurate diagnosis. Permitting any individual to engage in competitive athletics demands skill and judgment on the part of the doctor.

Cardiologists urge that any history or clinical evidence of rheumatic or congenital cardiovascular disease be systematically investigated and evaluated. The physical activities of children with functional heart murmurs have, at times, been unnecessarily restricted.[1] It behooves the examining physician to determine if these heart murmurs are in fact disabling before he disqualifies the youngsters. A youth with mild mitral insufficiency may be permitted to participate in a sports program that does not require constant strenuous effort or body contact. Rigorous sports such as swimming, track, tennis, football, boxing, wrestling, soccer, and hockey should, of course, be forbidden, but golf, baseball, and volley-ball, in which effort alternates with relaxation, may be permitted.

Primary aortic disease or a combination of aortic and mitral disease should disqualify a candidate for competitive sports. When the diagnosis of the suspected cardiac condition is beyond the skill and experience of the team physician, consultation with a cardiologist is essential. We encourage diabetic teenagers and adults to participate in athletics such as calisthenics, baseball, basketball, golf, and tennis. However, diabetics should be informed that strenuous exercise results in the production of more endogenous insulin; hence more food or less exogenous insulin should be taken at that time. Diabetic athletes should learn to anticipate episodes of hypoglycemia and to take extra carbohydrates during sport activities. One diabetic tennis champion, for example, drinks sugared soft beverages between games.

Protection

Head Injuries.—Participants in boxing, wrestling, football, and lacrosse, all sports that subject the head to cuffing and blows, should have electroencephalograms made before, during, and after the sports season.[2] The electroencephalograph can detect intracranial damage before it becomes clinically apparent.[3] An abnormal encephalographic reading has been deemed sufficient cause to suspend the license of a professional boxer before intracranial damage became apparent clinically. In many instances, late-appearing neurological disability and possibly even death have been averted by this procedure; many additional accidents and fatalities could be prevented by more widespread use of this diagnostic aid.

Eye Injuries.—All sports candidates and players must have complete visual examinations. The need for corrective lenses does not, of itself, disqualify a player; the extent of visual deficiency and the type of sport will determine his fitness. Such sports as baseball and track are suitable for players with limited vision. Boxing should be forbidden to the severely myopic, since direct blows to the eye may cause retinal detachment. Shatterproof lenses can be incorporated into football guards and are also useful in basketball. Lens guards are less satisfactory, since players find them clumsy. Contact lenses are often satisfactory. A player with useful vision in only one eye would do well to avoid all sports involving a risk of physical injury; the danger of total blindness is too grave.

Teeth Injuries.—Persons who wear braces or other oral prostheses may engage in athletics that involve bodily contact provided they wear mouthpieces of soft vulcanite or acrylic material. These, covering both upper and lower teeth, can be light in weight and inconspicuous and will help to prevent fractures of the teeth, lacerations of the lips and gingival tissues, and even devitalization of teeth by trauma. Mouthpieces should be worn by all contestants in contact sports.

Disqualifying Conditions

Numerous congenital and acquired orthopedic and neurological conditions may be considered disqualifying; these include scoliosis, spina bifida occulta, sacralization, lumbarization, flat feet, Klippel-Feil syndrome, atrophy of appendical and axial skeletal parts, absence of parts, osteomyelitic involvement, fragmentation of tibial tubercle, tremors, tics, fibrillation, and chorea. An obviously abnormal gait of neurological origin should disqualify a candidate. Persons with ataxic, spastic, or cerebellar gaits do not belong in competitive sports; neither do persons with clinical or electroencephalographic evidence of epilepsy. Dystonia is also disqualifying. Some braces, appliances, and prostheses are a hazard to both wearer and opponent, and users of potentially dangerous prostheses must be ruled out of body-contact sports.

When the physician forbids a candidate to participate in sports, the reasons must be made clear to the candidate himself and to all those concerned with the program; much misunderstanding and resentment will be avoided

if the team doctor maintains a policy of frankness and clarity in his dealings with coaches and players. Ultimately, the decision as to whether a candidate may participate in a sport rests on the physician's judgment. Humans vary so greatly in their capacity for adjustment and achievement that inflexible rules are unfair as well as impractical. Men and women with severe physical disabilities have competed with nonhandicapped players and have often won prominence in highly competitive sports. The wise physician will view the candidate as a total human being, not as a set of symptoms, when determining eligibility for sports.

Conditioning Players

In all sports, conditioning is of primary importance for the prevention of injuries, and the provision of protective equipment is next in importance. In football, it has been found that poor physical condition of players, poor equipment, faulty playing technique, and accidents are, in that order, the chief causes of injuries.[4] In my experience, individuals who are obese, awkward, considerably underweight, or ill-trained suffer the greatest number of injuries. The athlete who is well-muscled and properly conditioned rarely requires medical treatment for injuries.

Thorndike [5] advocates "diet, sleep, graduated muscular exercises and the absence of all drugs" as the foundation of a conditioning regimen. Conditioning requires the joint efforts of physicians, coaches, trainers, and dietitians. Nutrition is best regulated with training-table arrangements; when athletes take meals at home, as in secondary schools, the parents should be advised about adequate diet. The team physician should supervise the conditioning program so that players progress to their physical primes. The physician should inform coaches and trainers about fatigue symptoms, so that the condition is not permitted to become serious. Considerable medical wisdom is required to treat an athlete who is in a state of exhaustion. Proper conditioning will ensure performance at top skill and with minimal physical risk.

Protective Equipment

The team physician must demand that the coach or his assistants personally check to make sure that proper protective equipment and any indicated special paddings are worn for all sports. The plastic caps now being used by baseball players are as effective in reducing head injuries as the headguards used by boxers and football and lacrosse players. For some sports, it may be necessary to use special protective devices for the mouth, exposed and vulnerable joints, hands, genitalia, and sore areas to supplement the protection offered by uniforms. In football and basketball, players' ankle joints are taped to give the ligaments additional strength. The hands and wrists of boxers must be properly wrapped to prevent sprains of the wrist and metacarpophalangeal joints and, in the event of fracture, to prevent serious displacement of the bone ends. Mouthpieces worn in boxing as well as in football, lacrosse, and hockey permit diffusion of the power of a blow to the chin, thus diverting the force from the vital brain structures at the base of the skull.

For sore or weakened parts, special pads, often homemade, can be used. These serve best when applied directly to the skin. For example, a thigh guard taped directly to the skin offers more protection than one that is part of a uniform. When adhesive tape is used for protective strapping of the ankles, prior application of benzoin increases the adhesiveness of the tape and also serves as an antiseptic for cracks, fissures, and abrasions in the skin. Protection of the genitalia during noncontact sports is obtained with a plain fabric athletic supporter. For football, wrestling, basketball, hockey, and lacrosse, aluminum cups should be incorporated in the supporters. Boxers need still more protection for this region; they must use a rather elaborate device that fully protects the dependent structures of the lower part of the abdomen as well as the genitalia.

Treatment of Athletic Injuries

Although a detailed discussion of treatment cannot be included here, some basic principles should be noted. Most injuries are to the muscles and ligaments; these are best treated initially with pressure dressings and cold compresses. Rest of the injured part and such physical therapy measures as heat, massage, and exercise will improve circulation. Healing is thus hastened, adhesions are minimized, and muscle tone is retained. Adhesive tape should not be used for injured joints or where there is danger of swelling; an elastic bandage is applied to the injured area. Bruises of the face, ears, and head, frequent in football, lacrosse, and water polo, are treated with ice packs for one-half to one hour. After boxing bouts, trainers should apply cold compresses to the fighter's face, ears, and head to prevent the swelling, with its hemorrhagic exudates, that leaves fighters with marred faces and "cauliflower" ears. No physician should ever use procaine (Novocaine) hydrochloride or other agents to render an injured area analgesic so that an injured player can continue in action.

The contestant who has been ill or injured should be readmitted to participation only on the written recommendation of a physician. The readmitted player must be observed carefully by the coaches and the physician promptly informed of any deterioration of the player's condition. The doctor must follow his charges, especially if they are young, because adolescents generally dislike to report their aches and pains. Systematic, conscientious medical supervision during and after the playing season will help to prevent or minimize permanent disabilities from athletic injuries.

A well-equipped first-aid kit should be available at all games. Also, during body-contact events each team should have a light stretcher ready for use if necessary. An ambulance, parked out of the view of spectators, should be kept in readiness at football games. Police and fire departments can also be enlisted for emergency transportation service. Immediate, skillful, nontraumatizing care of an injured athlete may make the difference between mild and serious disability. All too frequently, well-meaning trainers, coaches, and officials cause more disability than they prevent.

The Ringside Physician

The first-aid techniques used by seconds at boxing matches are often fearfully primitive. Unskilled attempts to stop periorbital and other facial bleeding with unsafe

coagulants and unsterile materials can leave boxers with permanent, potentially infectious, lumpy fibrotic sites. Brutal handling of tissues by well-meaning but untrained assistants is not uncommon. Attempts to move a boxer with a spinal injury can result in severe permanent disability or even in death.

The ringside physician must order managers and handlers to avoid moving the head and neck of a floored boxer. Such manipulation, when done by unskilled persons, may result in more injury than that sustained by the boxer from the blow that felled him. The second should not be permitted to do anything to an unconscious fighter except remove the mouthpiece; all other first aid should be administered by the ringside physician. Immediate hospitalization for evaluation and treatment is indicated when the following conditions are present: persistent dilation or irregularity of the pupils or absence of the response to light; loss of contact with environment, as observed by direct examination and confirmed by testing the patient's responses to simple questions; and epileptiform movements of one or more extremities.

The ringside physician must advise the referee to halt any match in which one participant seems helpless against severe punishment; continued blows to a defenseless fighter endanger his life. Since referees are often unable to recognize just when a fighter becomes helpless, the ringside physician should be given the legal right to terminate a bout without the approval or consent of the referee. Only a physician can properly evaluate the effect of blows to the head, chest, or abdomen. He should not wait to be called into the ring by the referee but should be at the side of an injured fighter before handlers can use unskilled methods of treatment. After a decision match, the doctor should check both boxers for significant injuries before they leave the ring. Further examination in the locker room or in the doctor's office may be indicated.

The Football Physician

In football as well as in boxing, transportation of an injured participant may make the difference between a temporary and a permanent disability. Again, only the physician is equipped to deal with a player who has been hurt. When the doctor observes that a fallen player does not rise immediately, he should rush to the field without waiting for an official summons. This attitude on the part of the team physician not only lessens the effects of injuries but helps build morale among the team members.

The team physician should carry perles or capsules of aromatic spirits of ammonia with him; frequently, these will be all that is needed to put an athlete back in action. When there is some doubt about the nature or extent of the injury, the player should be taken out of the game until the doctor is able to make a decision about whether it is safe to continue playing; the doctor's decision must be conservative and weighted on the side of caution. When a taped joint has been injured, the doctor should remove the tape prior to examination. Circulatory complications may result from tape left on an injured part.

Physicians and Competitive Sports

Physicians should generally encourage participation by young people in competitive sports. Sports enhance health and develop physical capacity; also, team playing encourages cooperation, leadership, and a spirit of fair play. The so-called athletic heart is a misnomer, and physicians need not worry about it.[6] The enlarged heart of the highly conditioned athlete is a temporary compensation for an increased load, and the heart resumes normal size with the cessation of training. Handball players in their 30's need not forego this sport but should, instead, sensibly decrease the physical demand on the heart.[7] The pulse rate, the amount of perspiration, and the degree of thirst are guides, and a sportsman who observes and heeds these symptoms and paces himself accordingly can continue in athletics well into his later years.

Doctors have singled out football and boxing for special criticism, and numerous reforms based on medical opinion have been made. It is interesting to note that in 1938, long before the current reforms, Abe J. Greene, New Jersey athletic commissioner, quietly lifted the licenses of hundreds of boxers whose records indicated that they had risked serious permanent injury by continuing to fight. Martland's [9] classic analysis of the "punch-drunk" syndrome has been challenged recently in a report on professional fighters by Kaplan and Browder.[10] These observers state that head blows received during a properly conducted match rarely produce detectable brain injury, since most blows to the head are short of their mark or are deflected by the opponent. Gonzales [11] noted that there were twice as many fatalities from baseball as from boxing or football in New York City from 1918 to 1950.

Summary

Physicians, coaches, and administrators must cooperate to ensure that sports are conducted in the best interests of the participants. The responsibilities of the team physician should be clearly defined and understood by all persons concerned with team management. Reduction of the frequency and severity of sports injuries depends on cooperation among personnel, continued improvement of uniforms and equipment, and thorough conditioning of players. First aid for boxing and football injuries should be given only by the doctor in attendance. Participation in sports programs enhances the physical and moral development of young people and should be encouraged. The doctor's responsibility is to further the continued improvement of techniques for safe and healthful playing.

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DEATHS FOLLOWING ELECTROTHERAPY

REPORT OF FIVE DEATHS, WITH AUTOPSY FINDINGS IN FOUR CASES

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• *Deaths associated with electroconvulsive therapy given in a state hospital occurred in 5 instances out of a series of about 70,000 treatments given to 5,325 patients. The deceased patients were three men and two women, and their ages ranged from 38 to 57 years.*

Autopsies were obtained in four of the five cases and yielded evidence of coronary artery disease that had not been clinically evident. These deaths were not predicted or predictable.

The fatality rate is low, and the figures express the inherent risk of treatment. Nevertheless, the possibility of alleviating the cardiovascular strain of this treatment by the use of oxygen, of various drugs, and of various other modifications of the technique should receive attention.

Electroconvulsive therapy and its modifications carry a small but significant case fatality rate.[1] This rate, which is, however, not precisely known, has been estimated to be on the order of one death per 1,000 patients treated. A threefold range in either direction from this estimate, i. e., from one death per 3,000 patients to one death per 300 patients, should, we think, be considered acceptable in view of the inherent risks of treatment. The case fatality rate is apt to increase as a higher proportion of poor-risk patients are treated.[1c] Failure to accept and make known this risk in treatment has unfortunately given rise to the impression that electrotherapy for psychiatric illness is practically devoid of such hazard; this in turn has led willy-nilly to the erroneous assumption that death associated with treatment must in some manner be the fault of the psychiatrist giving the treatment or the institution involved or both. It is our plea that deaths in electroconvulsive and related forms of treatment be reported. It is only in this way that the actual case fatality rate can be established. This is, among other things, an important factor in the assessment of the relative merits of the several modifications of electroconvulsive therapy.

In contrast to the American practice in which deaths associated with electrotherapy are reported only sporadically, if at all, the rule in England and Wales is that all unusual or unexpected deaths, including those in electrotherapy and other somatic treatments (such as leukotomy, insulin, and continuous narcosis) that occur in psychiatric hospitals, come within the purview of the board of control of the Ministry of Health. This procedure, according to the Hon. W. S. Maclay,[1c] medical senior commissioner of the board of control, gives "an overall picture difficult to achieve in any other way. The information available is in the reports of death sent to the Board of Control, letters to Coroners, depositions at inquests, post-mortem reports and in some instances additional facts provided by the medical superintendents." In the four and a half year period beginning in 1947 there were 62 deaths in electrotherapy reported to the board of control. Of these deaths, over one-half (35) were in persons over the age of 55 years; in contrast only 6 were persons under 35 years. Two-thirds (or 41) of the 62 deaths were attributed to failure in the cardiovascular system; these include 4 due to intracranial vascular lesions and 3 due to pulmonary emboli. Not included in the above figures are five deaths that occurred in the special method of electronarcosis.

Although there is no comparable American report, we believe that the experience in this country is similar to that in Great Britain, since similar patients are treated by the same methods. Alexander,[2] in Boston, has pointed out that cardiovascular disturbances are the most dangerous complications of psychiatric electrotherapy. He has made a useful classification of cardiovascular accidents in treatment under four headings: acute heart failure (myocardial failure or infarction or both), vascular collapse, pulmonary edema, and disturbances of the cardiac rhythm. He has also ably discussed the management of these cardiovascular disturbances that may arise in treatment. Existing data clearly indicate that the case fatality rate in electrotherapy is disproportionately higher in older patients and that failure in the cardiovascular system is the leading cause of death in treatment. This failure is the result of the inability of the circulatory mechanism to withstand the suddenly increased demands made, or the strain imposed, at the time of treatment.

In the six-year period beginning in April, 1949, there have occurred at Rockland State Hospital five deaths associated with electrotherapy (table 1). During this period 5,325 patients were treated. This yields a case fatality rate of one death per 1,065 patients. These 5,325 patients were given a total of about 70,000 treatments, which yields a treatment fatality rate of one death per 14,000 treatments. These figures reflect in a statistical sense the inherent risk of treatment. The treatment fatality rate reported above is identical with that of another recent study, in which there was also reported a total of five deaths in 70,000 treatments.[3] Inspection of table 1 shows that in the five Rockland State Hospital fatalities both sexes are represented (three men and two women); that the patients' ages ranged from 38 to 57 years, with the median age of 44 years; that death occurred from the 1st to the 56th treatment, with the median being the 14th treatment; and that both the conventional (alternating current) technique (four cases) and the unidirectional current technique (one case) were used. In case 4, because of a marked skeletal deformity, myoneural block-

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ade with gallamine (Flaxedil) triethiodide was used.[4] Except for skeletal deformity in the patient of case 4 and moderate hypertension in the patient of case 5, all the other findings in the pretreatment examinations, including the results of the various laboratory tests, were within normal limits. It is of course generally recognized that neither of the above conditions, skeletal deformity or hypertension, is a bar to treatment.[5]

The guiding principle in deciding whether a course of electrotherapy should be given is for the psychiatrist to compare the risk of nontreatment with the risk of treatment. The risk of nontreatment may well exceed the risk of treatment; this is most likely whenever the patient is severely depressed or deluded. This arises from the fact that the untreated or inadequately treated mental illness may result in suicide and also from the fact that the untreated illness may in itself impose a greater burden on the circulatory system than the proposed course of treatment. Successful treatment ends suffering, which might otherwise be intolerable.[6]

Careful examination of the hospital records, from which the essential data in table 1 are derived, yields no advance clue that these five treatments would end in death. These fatalities were not only unpredicted; they were unpredictable. In our series of five cases, only one death (case 1) followed the first treatment. This is in contrast to the larger British experience, as reported by Maclay,[1c] in which almost one-half of the deaths occurred after the first treatment. In the Rockland State Hospital series, the other four patients (cases 2 through 5) had received before death at least nine treatments (which would incidentally represent an average course for the treatment of a mental depression); in these cases the assumption was clearly justified that the required course of treatment could have been completed without undue risk.

In four of our cases (all except case 5) autopsy was performed. The significant positive findings are presented. These add considerably to the value of a report, and we urge that such findings generally be published.

Findings at Autopsy

CASE 1.—This patient was a man, 54 years old. In the brain there was a slight cortical atrophy (brain weight not recorded). There was a moderate atherosclerosis of the vessels at the base of the brain. The heart weighed 400 gm. The right ventricle was hypertrophied. There was an advanced atherosclerosis of the coronary arteries, which on serial section were found to be little more than calcific tubes with barely patent lumens. The aortic and mitral valves were thick and calcific. There was a patchy atherosclerosis of the aorta. The complete pathological diagnosis was generalized arteriosclerosis with arteriosclerotic heart disease, coronary sclerosis with partial occlusion (insufficiency), pulmonary congestion, and atrophic cirrhosis of the liver.

CASE 2.—This patient was a woman, 44 years old. The brain weighed 1,250 gm., which is 100 gm. less than the average for a person of this patient's size. The arteries at the base of the brain were small in caliber. The heart weighed 310 gm. There was an early atherosclerosis, with resulting decreased caliber of the coronary arteries. The middle portion of the main branch of the left anterior coronary artery was completely occluded by a fresh thrombus. Surrounding the occluded vessel, there was a red area of fresh infarction. The aorta and the other main vessels were smaller than usual. The pathological diagnosis was coronary sclerosis with fresh coronary thrombosis and early myocardial infarction and hypoplastic vascular system. This patient had received 55 treatments without mishap. Recently there has been reported elsewhere the death of a 72-year-old man within a few minutes after his 51st treatment; at autopsy, coronary

TABLE 1.—*Analysis of Five Deaths That Occurred in Electrotherapy*

Case No.	Age, Yr.	Sex	Diagnosis	Physical Status	Treatment That Ended in Death	Pretreatment Medication	Autopsy
1	54	M	Involutional melancholia	Within normal limits B. P. 140/85 mm. Hg Chest x-ray normal ECG normal	1st treatment Conventional (a. c.) technique, 130 volts for 0.8 sec., yielding generalized convulsion Initial recovery uneventful; 65 min. later, sudden cyanosis, pulse feeble; death 15 min. later (80 min. after therapy) *	None	Yes
2	44	F	Schizophrenia, catatonic type	Within normal limits B. P. 150/90 mm. Hg Chest x-ray normal ECG normal	56th treatment (55th treatment given ½ hr. previously with normal recovery) Conventional (a. c.) technique, 140 volts for 0.4 sec., yielding generalized convulsion Normal recovery until about 10 min. after, when patient suddenly ceased to breathe and became pulseless and cyanotic; pronounced dead 85 min. after treatment	None	Yes
3	38	M	Schizophrenia, paranoid type	Within normal limits B. P. 140/80 mm. Hg Chest x-ray normal ECG not done	14th treatment Unidirectional current technique, with mild generalized seizure ensuing at 15 ma.; seizure, lasting 40 sec., controlled with 5 ma. At end of seizure, patient failed to breathe; no pulse or heart sounds were detected; pronounced dead 45 min. after application of electric stimulus	None	Yes
4	57	M	Schizophrenia, paranoid type	Marked kyphoscoliosis; otherwise within normal limits B. P. 140/90 mm. Hg Chest x-ray normal ECG normal	9th treatment Conventional (a. c.) technique, 130 volts for 0.3 sec., yielding mild generalized seizure At end of seizure, patient failed to breathe; no pulse or heart sounds were detected; pronounced dead 45 min. after treatment †	Gallamine (Flaxedil) triethiodide 40 mg. I. V. followed by prostigmine 0.5 mg. I. M.	Yes
5	41	F	Involutional psychosis, paranoid type	Essential hypertension; otherwise within normal limits B. P. 180/120 mm. Hg Chest x-ray normal ECG normal	21st treatment Conventional (a. c.) technique, 140 volts for 0.4 sec., yielding generalized seizure Patient breathed spontaneously and without difficulty immediately after treatment; during transfer from treatment table to bed, she ceased to breathe and was pulseless; pronounced dead 45 min. after treatment	None	No

* This is the longest interval between treatment and death in this series.
† This is the only case in the series in which myoneural blockade was used.

arteriosclerosis with thrombosis and an old myocardial infarct were found.[7] "The coronary arteries are described as showing obliterating disease and the lumen was frequently narrowed to pin-point size. In retrospect one may wonder how this patient tolerated 50 treatments without apparent disturbance."

CASE 3.—This patient was a man, 38 years old. The brain weighed 1,570 gm. The excess weight was largely due to edema, which partially filled the cerebral fissures. The cortical veins were engorged with dark blood. The arteries at the base of the brain were small, and their terminal branches appeared insufficient for normal blood passage. The heart weighed 240 gm. Although the heart was smaller than usual, there was a marked compensatory hypertrophy of the dilated left ventricle. There were diffusely scattered petechiae over much of the myocardium that were especially noticeable on the anterior aspect of the left ventricle and the lateral and superior aspect of the right ventricle. There was an early atherosclerosis of the ascending aorta. This process encroached on the ostiums of the coronary arteries. The endocardium, particularly of the aortic and mitral valves, contained yellow, patchy elevations of early atherosclerosis. The caliber of the coronary vessels was abnormally small, so that the lumens of the main coronary vessels in their distal halves were practically obliterated. All the blood vessels examined, including those of the brain, spleen, kidneys and mesentery, were small. The histopathological report stated that there was a pronounced fragmentation of the myocardium; this was associated with a few foci of lymphocytes and eosinophils. There was a marked thickening of the media of an imbedded branch of a coronary artery. There was also a perivascular infiltration, mostly lymphocytic, of this arteriole as well as a fibroblastic proliferation of the internal elastic membrane. The complete pathological diagnosis was arteriosclerotic heart disease, coronary sclerosis with partial occlusion (insufficiency), hypoplastic vascular system, and cerebral edema.

CASE 4.—This patient was a man, 57 years old. The brain weighed 1,430 gm., and it was slightly edematous. A few scattered petechiae were found on sectioning the brain; these were mostly in the white matter near the basal ganglions. There was a moderate atherosclerosis of the intracranial vessels. The heart weighed 350 gm. There were moderately advanced degenerative changes of the myocardium. There was an increased deposition of fat in the myocardium of the right ventricle. There were signs of brown degeneration of the hypertrophied left ventricle, which presented, on serial section, a widespread patchy and streaky fibrosis. Advanced coronary sclerosis had caused an almost complete occlusion of the anterior main vessel in its distal half. This vessel was so stiff that it could be bent and broken like a broom straw. Similar but less marked sclerotic changes were seen in the other main vessels, including those forming the circle of Willis and extending into the brain. Atherosclerotic plaques, which surrounded the ostiums of the coronary vessels, had further reduced their capacity. There was a marked atherosclerosis of the aortic and mitral valves that caused a partial stenosis of the mitral valve. There was an advanced atherosclerosis of the aorta and its large branches to such an extent that large plaques could be scaled from the intima. The pathological diagnosis was generalized atherosclerosis with arteriosclerotic heart disease, coronary sclerosis with partial occlusion (insufficiency), and cerebral edema and petechiae.

In all of the above four cases there was evidence at autopsy of coronary artery disease or insufficiency, which had not been clinically evident. (In the only patient in the series with known cardiovascular disease, the patient in case 5 with essential hypertension, permission for autopsy was not obtained.) Our comments on the causes of death in this series of cases will be restricted to the four cases in which autopsy was performed. The existence of the chronic lesions of coronary sclerosis does not prove that these lesions were the cause of death associated with electrotherapy. These lesions may perhaps be more correctly regarded as the pathological background or substrate of the events that led to death in treatment. Undetected, including undetectable, coronary sclerosis is, we believe, the most important concealed risk in psychiatric electrotherapy. This situation is one that must be clearly recognized and accepted as a "calculated risk" in treatment. It is probably desirable to explain this fact to members of the patient's family. We see no reason to harass the patient with this unpleasant information, unless he is one who insists on the whole truth.

Analysis of the mode of death in the four cases with autopsy indicates that in the patients in cases 1 and 2 the initial recovery from treatment was uneventful and death occurred unexpectedly some minutes later (table 1). The sequence of events strongly suggests that these deaths were due to acute circulatory failure. Referring again to the abbreviated autopsy protocols, it is seen that in the patient in case 1 there was advanced coronary sclerosis and that in the patient in case 2 there was coronary sclerosis with a fresh coronary thrombosis. It must be recognized in the patient in case 2 that the coronary thrombosis may have arisen during the agonal process and may have been, as it were, a manifestation rather than a cause of death. This is mentioned merely to illustrate the complexity of the problem of deciding the cause of death in electrotherapy. The important fact is that electrotherapy creates a suddenly increased demand or a strain on the circulatory system and, in the presence of a coronary circulation already impaired by atherosclerosis, the heart may be unable to meet these added requirements. Several important aspects of this cardiovascular strain in electrotherapy will be briefly described; first, however, cases 3 and 4 need to be further considered with respect to the mechanism of death.

Mechanism of Death

In cases 3 and 4, the patients did not recover from the treatment, although each patient had responded satisfactorily to several prior treatments. In both instances there was respiratory as well as circulatory failure; also in both cases there were brain lesions of doubtful significance. Certainly respiratory failure cannot be excluded as the cause of these deaths, although it is obvious that the circulatory failure immediately following treatment is in itself an adequate explanation of these fatalities in treatment, particularly in view of the degree of coronary sclerosis found in both cases. Again we believe that these are instances in which an impaired coronary circulation, which was found at autopsy, was unable to meet the increased demands made in treatment.

In addition to the inherent risk imposed by the presence of coronary sclerosis, it must also be recognized that electrotherapy may result in death because of its adverse effect at the time of treatment on the initiation and conduction of the cardiac impulse.[8] These treatment-induced cardiac arrhythmias are divided, according to their origin, into two groups: vagal and extravagal. A classification based on the relative severity, in our experience,[8] is shown in table 2. The vagal arrhythmias are characterized by cardiac slowing and even standstill; they are uniformly preventable by adequate atropinization (usually, 1.2 to 2.4 mg. of the sulfate). The extravagal arrhythmias are in general characterized by the occurrence of ventricular premature contractions; in the more severe

forms there may be ventricular tachycardia leading to disruption of the basic cardiac rhythm. The control of these extravagal arrhythmias, unlike those of vagal origin, is now only partially obtained. Quinidine has been found useful but not consistently so.[9] Chlorpromazine may also prove to be helpful in this respect.[8] It is likely that the adverse effects of these treatment-induced arrhythmias on the circulation are aggravated by the presence of coronary sclerosis, thus leading to acute heart failure in treatment. This may serve to illustrate our conception that death in treatment is more commonly the result of a concatenation of factors, some chronic (such as coronary sclerosis), others acute or treatment-induced (such as these rhythm disturbances, paroxysmal hypertension, hypoxia, and the increased work of the heart).

Paroxysmal rises in the arterial and venous pressures, which immediately follow the application of the electric stimulus, are another manifestation of cardiovascular strain in treatment.[10] These sudden elevations must be regarded as potentially dangerous, particularly in the treatment of a patient suffering from severe hypertension or advanced atherosclerosis. It has not been proved, however, that these paroxysmal rises are a direct or contributory cause of death in treatment, but they should be suspected, we believe, especially whenever such deaths are associated with intracranial hemorrhage. In Maclay's [1c] series, three deaths are attributed to intracranial hemorrhage, but the author does not relate these deaths to the paroxysmal rises in blood pressure during treatment. Tentative results from a study now in progress indicate that the severity of treatment-induced arterial hypertension may be much reduced by the intravenous injection, shortly before electric stimulation, of 200 mg. of tetraethylammonium chloride.[11] Since this drug produces its effect through a blockade of the autonomic ganglions, it is also likely that it will reduce the incidence and severity of treatment-induced cardiac arrhythmias.

TABLE 2.—*Treatment-Induced Cardiac Arrhythmias Classified According to Severity*

Severity	Arrhythmias
Mild	Atrial premature contractions Scattered ventricular premature contractions (VPC) Short runs of VPC Occasional short pause
Moderate	Frequent VPC with long runs of bigeminy or trigeminy Asystole up to 2½ sec.
Severe	Frequent VPC of varying patterns with beginning disruption of the basic cardiac rhythm Asystole from more than 2½ to 5 sec.
Very severe	Disruption of the basic cardiac rhythm Ventricular tachycardia Asystole for more than 5 sec.

In addition to the adjuvants already described (atropine, chlorpromazine, quinidine, and tetraethylammonium chloride), there are a variety of other drugs and procedures that may be used in the effort to alleviate cardiovascular strain in treatment. Variations in the mode of electric stimulation, such as modified electroconvulsive therapy with unidirectional current, focal and nonconvulsive treatments, have been recommended, but their alleged advantages over the conventional or Cerletti-Bini technique are disputed.[12] Prominent among the other adjuvants are oxygen insufflation, myoneural blockade (particularly by succinylcholine), intravenously administered barbiturate anesthesia, digitalis preparations, hypotensive drugs, and various ganglionic blocking agents.

The amount of work done by the patient during the seizure (as measured by oxygen consumption) is significantly reduced whenever the treatment is carried out under intravenously administered barbiturate (thiopental) anesthesia.[13] This work may be abolished, i. e., the oxygen consumption reduced to resting levels, if the treatment is given under the combined modification of the barbiturate anesthesia and succinylcholine blockade. Hypoxia can then be prevented whenever 100% oxygen insufflation is used with this combined method. A similar technique and its advantages for modifying electrotherapy with atropine–intravenously given barbiturate–succinylcholine–oxygen insufflation have been recently described elsewhere.[5] This summing-up illustrates the approaches used in dealing with the problem of cardiovascular strain and the other complications of psychiatric electrotherapy.

Summary

Electroconvulsive therapy and its modifications carry a small but significant case fatality rate, which is estimated to be on the order of one death per 1,000 patients treated. The main cause of death in treatment is the failure of the circulatory system to withstand the suddenly increased demands, or the strain imposed, at the time of treatment. The case fatality rate is higher in older patients and in those with cardiovascular disease or disability. Less frequently death in treatment is attributed to failure in the respiratory and nervous systems; even within these systems the fatal lesion is apt to be vascular or secondary to cardiovascular lesion. In the four cases in this series in which autopsy was done, coronary sclerosis with resultant partial or complete occlusion (in one case, a fresh thrombus) was found. In these four cases death was attributed to the inability of the impaired coronary circulation to withstand the suddenly increased demands associated with treatment. No other significant lesions that could account for death were found. These coronary lesions were not detectable by the usual methods of pretreatment examination, including electrocardiography. For these reasons these deaths were not predicted or predictable.

Much attention is now directed at the alleviation of the sources of strain in treatment. But the inherent risk of treatment cannot at present be eliminated, largely because of the presence of undetected coronary artery sclerosis and its effect upon the cardiovascular responses to electric stimulation. Despite these complications the case fatality rate in psychiatric electrotherapy is low; whenever treatment is indicated, this fact should as a rule outweigh other considerations, provided adequate precautions are carried out.

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NEUROPSYCHIATRIC SEQUELAE OF PREMATURITY

A LONGITUDINAL STUDY

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• *The physical and mental status of 992 infants was studied with the help of the Gesell developmental examination and a physical examination, so as to compare 500 single-born premature infants with 492 infants born at term. The comparison was made at age 40 weeks for the full-term infants and at the corresponding corrected age for the premature infants. The two groups were matched as to race, socioeconomic status, and other significant factors.*

The incidence of abnormalities was found to increase as the birth weight group of the infant decreased, so that 50.9% of the infants with a birth weight less than 1,501 gm. had defects ranging from minor neurological damage to severe intellectual deficiency. Some of these also had major visual handicaps.

The association of complications of the prenatal and paranatal periods with fetal and neonatal mortality has been known for a long time, as has the relationship of these conditions to cerebral palsy.[1] Recent retrospective epidemiological studies have extended these associations to other neuropsychiatric conditions and have led to the postulation of a "continuum of reproductive casualty" resulting from brain damage, with a lethal component consisting of abortions, stillbirths, and neonatal deaths and a sublethal component with a gradation of damage extending from cerebral palsy [2] through epilepsy [3] and mental deficiency [4] to the minor dysfunctions that could result in behavior disorder[5].

Prematurity is one of the major hazards of the paranatal period, and its relationship to fetal and neonatal death is unquestioned. The course of development and adjustment of those premature infants who survive is not so clearly defined. Dunham [6] and Alm [7] in their reviews of the literature have indicated that the available information is in many instances contradictory. They have pointed out that the studies are hampered by lack of sufficient control groups, by the difficulties of adequate follow-up studies, by the absence of objective measures of progress, by the prejudices introduced by the selection of small groups of infants from individual hospital services, and by the use of the retrospective method of securing information.

The present report presents an anterospective study of a group of premature infants and full-term control infants and is concerned with an evaluation of neurological status and intellectual potential of this group of infants at 40 weeks of age.

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Method of Study

This inquiry is part of a study of the 4,700 premature infants born in Maryland in 1952. It is restricted to a sample of resident infants born in Baltimore and still living there who were given a developmental examination at 40 weeks of age. The sample included 500 single-born premature infants, consisting of all available survivors whose birth weight was 1,500 gm. (3.3 lb.) or less, with the remainder selected by a predetermined design from the weight groups between 1,501 and 2,500 gm. (3.3 to 5.5 lb.) on the basis of hospital of birth and area of residence. The census tracts, geographical areas of the city defined by the U. S. Bureau of the Census, are crudely homogeneous as regards the economic composition of their inhabitants. They were divided into 10 groups on the basis of median rental so that one-tenth of the white population fell into each of the 10 groups. On the basis of residence of the child an economic tenth was assigned and the socioeconomic status roughly determined. All socioeconomic groups were included in the sample. The sample also included 492 full-term single-born control

infants who were matched to the premature infants for race, season of birth, parity of mother, hospital of birth, and socioeconomic status. Careful preparatory steps, to be described elsewhere, were taken to inform the hospitals, health departments, physicians, and parents of the selected infants about the study in order to gain optimal cooperation.

Examinations were scheduled for 1,170 infants. The 992 infants who were included in the final group of babies studied represented an 85% completion of the examination for all of the infants who were given appointments; 3.5% were refusals, while the other 11.5% could not be located. Table 1 shows the distribution of the 992 infants by race and birth weight groups and indicates that a significantly higher percentage of the nonwhite infants were in the lower weight groups, particularly in those between 1,001 (2.2 lb.) and 2,000 (4.4 lb.) gm. (chi square = 9.79; $p < 0.05$ on 4 degrees of freedom). (In judging the evidence on this and subsequent questions a 5% level of statistical significance was used.) Four hundred thirty-five, or 43.9%, were white. There were no significant differences between the premature and the control infants for either education of the mothers or economic fifth

TABLE 1.—*Weight Distribution, by Race, of Premature and Full-Term Control Infants*

Weight Group, in Gm.	White, %	Nonwhite, %	Total, %
1,000 or less	0.9	0.5	0.7
1,001-1,500	3.2	6.5	5.0
1,501-2,000	6.7	9.9	8.5
2,001-2,500	37.9	34.8	36.2
Subtotal for premature infants	48.7	51.7	50.4
2,501 or more (control)	51.3	48.3	49.6
Total	100.0	100.0	100.0

of residence as determined by census tract, indicating that the socioeconomic status of the two groups was comparable.

The examinations consisted of a Gesell developmental examination and a physical examination, and almost all of them were done by one of us (H. K.), a pediatrician experienced in this work, who was not told if the infant was premature or full-term, in order not to bias her observation of behavior or her diagnostic judgment, nor was she given any information about the child's history. In some instances the information was revealed unwittingly by the mother.

It was planned that each infant would be examined at 40 weeks of age. This could not always be accomplished, not only because of the difficulties in scheduling the necessary number of appointments in the time available but also because not all of the mothers could keep the first appointment made for them. Age at the examination therefore ranged from 34 to 69 weeks, with a median of 40 weeks and with 75% seen between 39 and 41 weeks. In the case of the premature infants, the chronologic age was corrected to make allowance for the amount of prematurity. A history was taken from the mother, usually by a person other than the pediatrician, and was recorded on a form devised for the purpose. It covered items such as neonatal adjustment, illness, seizures and other neurological symptoms, current emotional behavior, and some parental history.

The pediatrician's Gesell examination followed the procedure outlined in "Developmental Diagnosis."[8] A brief interview was conducted to ascertain the infant's current behavior. The questions concerned items on the Gesell developmental schedules not covered by the recorded history. The interview served three functions. It gave the examiner an idea of the general maturity level, so that she would know where to begin the examination sequences, it yielded information on behavior that would most likely not be elicited in the course of the examination, such as language and personal-social behavior, and, perhaps most important of all, it gave the infant a chance to adjust to the examiner, so that the ensuing examination could proceed smoothly. The standard examination items were offered, and the situations were adapted as necessary in the face of handicapping conditions or unusual emotional responses, and a dictated recording of the infant's behavior was made describing not only the use to which he put the examination materials but his neuromuscular patterning as he manipulated them. Gross motor activity was elicited at the end of the examination sequence. The infant's performance was recorded on the appropriate Gesell developmental schedule while the mother was undressing the infant for the physical examination.

After the baby was examined, weighed, and measured, a 40-week examination form was completed. This included general comments, an evaluation of the quality of integration, abnormal behavior patterns, abnormal neurological patterns, the physical examination, the assignment of maturity levels for the various fields of behavior, a diagnosis of neurological status and intellectual potential, and a prognosis for future development. Only after the examination record was completed was the history reviewed to see if there were any factors, such as severe convulsions or institutionalization, that might modify the prognosis made. Changes in prognosis were necessary on fewer than 10 occasions.

Two-thirds of the examinations were done in the study office, while most of the remainder were carried out at home because the mothers were unable for one reason or another to bring the infant in for the examination. When the examination was done at home or in a hospital, it was necessary for the pediatrician to take the history also, but this followed rather than preceded the examination and the judgments made, and the examiner asked the mother not to reveal the baby's birth weight.

The diagnostic category to which each infant was assigned by the pediatrician's clinical examination was the basis for comparing the development of the premature and the full-term infants. The neurological status was an estimate of the integrity of the nervous system as this was manifested by the absence or presence of impairment in neuromotor functioning and deviations in muscle tonus and control. It was expressed in terminology appropriate to the field of infant neurology that indicated the extent of departure from normal and comprised five categories. Those infants who were called "normal" were without signs of neurological damage, while those in an "indeterminate" category had such minor deviations from normal patterning that for summary purposes they were added to the normal group. Those infants who had "minimal damage" were a group with definite and distinctive

deviations in neurological patterning in which clinical experience with the examination technique indicated that there would be complete compensation and no detection of abnormal neurological signs later by the standard neurological examination. Another group called "possible cerebral palsy" were infants who had signs and symptoms that would warrant a diagnosis of cerebral palsy had they been observed in an older child. However, clinical experience indicated that, although most infants with this degree of abnormality at 40 weeks of age eventually would compensate completely and have no neurological residua, cerebral palsy could not be ruled out definitively. The final group with "overt abnormality" had gross deviations from normal neurological patterning and were expected to continue to present abnormal neurological signs.

The infants examined were not representative of the distribution of the surviving premature infants in the population, since all those under 1,500 gm. and only a sample of those between 1,501 and 2,500 gm. were selected. In order to derive an estimate of the distribution of the various diagnostic categories in the total surviving premature population, it was necessary to adjust the observed rates in accordance with the expected distribution of the surviving infants by weight groups. In the data presented, rates that refer to the total premature population are always adjusted or expected rates. Rates for specific weight groups are observed rates.

Neurological Status.—Table 2 divides the infants into three birth weight groups, 1,500 gm. or less, 1,501 to 2,500 gm., and over 2,500 gm., and compares the premature and the full-term infants by neurological

TABLE 2.—*Neurological Status at Forty Weeks of Age of Premature and Full-Term Control Infants*

Weight Group, in Gm.	No.	% in Each Diagnostic Category					
		Normal	Indeterminate	Minimal Damage	Possible Cerebral Palsy	Overt Neurological Defect	Total
1,500 or less	57	29.9	21.0	22.8	14.0	12.3	100.0
1,501-2,500	443	63.6	13.1	16.0	5.6	1.6	99.9
Subtotal for premature infants, adjusted for weight distribution	...	62.0	13.5	16.3	6.1	2.1	100.0
2,501 or more (controls)	492	78.0	10.4	10.0	1.9	0.6	100.0
Total	992	68.9	12.2	13.4	3.8	1.7	100.0

TABLE 3.—*Intellectual Potential at Forty Weeks of Age of Premature and Full-Term Control Infants*

Weight Group, in Gm.	No.	% in Each Diagnostic Category								
		Superior	High-Average	Average	Low-Average	Dull-Normal	Borderline Defective	Defective	Defect, Type Unclassified	Total
1,500 or less	57	...	5.3	57.8	14.0	5.3	5.3	8.8	3.5	100.0
1,501-2,500	443	1.8	14.5	69.7	9.5	2.7	0.5	1.1	0.2	100.0
Subtotal for premature infants, adjusted for weight distribution	...	1.7	14.0	69.1	9.7	2.8	0.7	1.5	0.4	99.9
2,501 or more (controls)	492	6.3	15.5	67.5	8.1	1.0	0.4	1.0	0.2	100.0
Total	992	3.9	14.4	68.0	9.1	2.0	0.7	1.5	0.4	100.0

The intellectual potential was a clinical estimate of intelligence based largely on the adaptive maturational status of the child. It took into account not only the developmental level but also the quality of functioning. It was expressed in the same terminology as that usually used in placing a child within or outside the average group and ranged from superior to defective.

Findings

The white infants appeared to have fewer cases of possible cerebral palsy, overt neurological abnormality, and intellectual defect and more cases in the minimal damage category or with above-average intelligence than the nonwhite infants when rates were calculated from the observed numbers. Because there were more nonwhite infants with low birth weights, the birth weight distribution of white infants was adjusted to that of nonwhites. When this was done, the differences disappeared. The racial groups, therefore, were pooled and infants compared on the basis of birth weight groups. Distribution of neurological diagnoses and of estimated intellectual potential was examined on this basis.

status. It shows a significant trend for all the weight groups. There was, in the total premature group, a lower expected percentage of normal (normal plus indeterminate) infants, 75.5% compared to 88.4% for the controls, as contrasted to a higher number of premature infants with minimal damage, possible cerebral palsy and overt neurological defect (chi square = 51.3; $p < 0.01$ on 4 degrees of freedom). The least premature infants with birth weights between 1,501 and 2,500 gm. also had a lower percentage of normal (normal plus indeterminate) cases (chi square = 31.5; $p < 0.01$ on 4 degrees of freedom) than the controls, while the most premature infant group in which the birth weight was 1,500 gm. or less had the highest percentage of babies with all degrees of neurological abnormality (chi square = 112.3; $p < 0.01$ on 3 degrees of freedom). For example, only 50.9% of the smallest infants were normal (normal plus indeterminate), compared to 76.7% for the larger premature infants and 88.4% for the controls. Of the premature infants with birth weights under 1,501 gm., 26.3% had neurological signs of sufficient severity (possible cerebral palsy plus overt neurological defect) to

warrant close developmental supervision in order to be certain about future development. The comparable incidence for the remainder of the premature infants was 7.2% and for the full-term infants 1.6%.

Intellectual Potential.—Table 3 divides the infants into the three birth weight groups and compares the premature and the full-term infants by intellectual potential. Again there were significant trends for all the weight groups. There was a lower expected percentage of above-average babies and a higher expected percentage of dull-normal and defective infants among the total premature infants than among the control infants (chi square = 24.1; $p < 0.01$ on 7 degrees of freedom). The least premature infants with birth weights between 1,501 and 2,500 gm. also had among them fewer above-average babies and more dull-normal and defective infants than the control infants (chi square = 16.2; $p < 0.01$ on 5 degrees of freedom), while the most striking differences were found in the smallest premature infants whose birth weights were under 1,501 gm. (chi square = 54.2; $p < 0.01$ on 4 degrees of freedom). To illustrate, 5.3% of the infants in the lowest birth weight group were above average, compared to 16.3% for the rest of the premature infants and 21.8%

TABLE 4.—*Total Deviations from Normal of Premature and Full-Term Control Infants*

Weight Group, In Gm.	No. of Cases	Abnormality, %
1,500 or less	57	50.9
1,501-2,500	443	24.5
Subtotal for premature infants, adjusted for weight distribution	...	25.7
2,501 or more (controls)	492	12.8

for the controls. Of the infants with birth weights under 1,501 gm., 17.6% were classified in the borderline defective, defective, or defect, type unclassified, range. The comparable incidence for the remainder of the premature infants was 1.8% and for the full-term infants 1.6%.

When overlapping of diagnosis between neurological damage and intellectual defect was eliminated, 20, or 35.1%, of the smallest infants whose birth weight was under 1,501 gm. were found to have possible cerebral palsy, overt neurological abnormality, intellectual defect, or a combination of these conditions; 3 of these babies were also blind as a result of retrolental fibroplasia. In addition, among the babies with only minimal damage, two others were blind and three more had serious visual handicaps resulting from this condition. This brought to 25, or 44%, the number of infants in this low-birth-weight group who at 40 weeks of age had an abnormal condition of sufficient magnitude to cause serious concern about the prognosis for future development. The comparable incidence for the rest of the premature infants was 8.6% and for the full-term infants 2.6%.

The over-all adjusted incidence of definite neurological defect (possible cerebral palsy plus overt neurological defect) in the premature infants was 8.2%, significantly higher than the rate of 1.6% in the full-term control infants. For mental defect (borderline defective, defective, and defect, type unclassified) the expected rate in the premature infants was 2.6%, not significantly different from the rate of 1.6% in the controls, although in the same direction. That this difference is nevertheless real is supported by the fact that, when the dull-normal infants are included, the total expected percentage of below-average babies among the premature group is increased to 5.4%, which is significantly higher than the comparable rate of 2.6% in the full-term control infants. It might be of interest to add that no infant with a birth weight under 2,001 gm. was considered to have a superior intellectual potential.

Table 4 summarizes all the deviations from normal. The abnormalities found ranged from minimal damage to blindness with mental deficiency. The smallest premature infants with birth weights under 1,501 gm. showed abnormalities in 50.9% of the cases. The group with birth weights between 1,501 and 2,500 gm. had an incidence of abnormality of 24.5%, while the adjusted rate for the total premature group was 25.7%. Of the full-term controls, 12.8% had abnormalities. The differences between the weight groups were statistically significant.

Comment

Recent epidemiological investigations have postulated an association between paranatal complications, prematurity, and the development of neuropsychiatric disabilities. They have also postulated a continuum of reproductive casualty that ranges from sufficient brain damage to cause fetal and neonatal death to the lesser degrees of brain damage extending from cerebral palsy down through the minimal damage that may result in subsequent behavioral dysfunction. The longitudinal anterospective approach can put both of these hypotheses to the test. The method involves selecting a group of infants with the condition the effect of which is to be evaluated, in this case prematurity, choosing a suitably matched control group, in this instance full-term infants, and following both groups as they grow to maturity to determine the incidence of disabling conditions. This initial phase in the longitudinal investigation of the effects of prematurity has answered in the affirmative the question of whether or not there is a relationship between prematurity and neuropsychiatric disability. At 40 weeks of age more premature than full-term infants have abnormal conditions of sufficiently serious degree to warrant careful developmental follow-up for diagnostic and prognostic purposes. A greater number of premature infants also have the lesser degrees of neurological involvement that, according to the hypothesis, are precursors of subsequent behavioral dysfunction. This relationship to behavioral dysfunction can be tested only by continuing to follow the group of children into the school years, when these disabilities can be expected to become manifest.

It is pertinent at this point to raise the question of the value of tests of infants in predicting future development, since previous investigators [9] have indicated that low correlations of about 0.2 or less are obtained between various psychological examinations at nine months of age and again at about three years. Reexamination of about 250 of the present study group has already been done at age three years, and the results will be presented in a subsequent communication. They indicate that, when the Gesell developmental examination is used as a neuro-

logical tool by a physician trained in its administration, the correlation between developmental quotients on infant and preschool examinations is high, about 0.5. In those infants diagnosed at nine months as clinically abnormal it is 0.75, indicating that it is effective in picking out infants in need of supervision. Tests of intelligence at three years of age are known to have significant correlations with school age tests.[9a]

The relationship of other maternal complications, particularly toxemia and bleeding, to neuropsychiatric dysfunction has not been elucidated by the present investigation, although the well-known fact that these complications of pregnancy are more frequent when the infant is born prematurely is confirmed. Since less than 10% of the mothers in the group had these complications and less than 10% of all the infants were seriously abnormal, further investigations similar to this study of each of the complications individually are necessary.

It is important to reemphasize here the high percentage of infants whose birth weights were under 1,501 gm. who were abnormal. Data from another phase of the study of premature infants[10] indicate that it is in the group of infants with birth weights between 1,001 and 1,500 gm. that the greatest increase in survival rate occurs when the infants are cared for in hospitals with services conforming most closely to the recommended standards for care of newborn and premature infants. This lends support to the concept that the main direction for efforts on behalf of prematurity lies in the area of prevention.

Consideration cannot be given here to other factors such as physical growth, educational background, and socioeconomic status that affect the course of development. Further reports on these subjects as well as on the relationship between the 40-week and three-year examinations are planned.

Summary

In order to study the effects of prematurity on the course of development, a Gesell developmental examination and physical examination was given to a group of 992 infants in Baltimore. These were 500 single-born premature infants and 492 full-term control infants who were matched to the premature infants on the basis of race, season of birth, parity of mother, hospital of birth, and socioeconomic status. All socioeconomic groups were included, and the 992 infants represented an 85% completion of all the examinations scheduled. Analysis of the findings shows that there is no significant difference between whites and nonwhites in the incidence of neurological and intellectual defect when adjustment is made for differences in weight distribution between the races. The incidence of abnormality increases as the birth weight group of the infant decreases. At 40 weeks of age, when the rates in the total premature population are adjusted according to the expected weight distribution of the surviving prematures, the expected over-all incidence of serious neurological abnormality (possible cerebral palsy plus overt neurological defect) is 8.2%, significantly higher than the rate of 1.6% in the controls. For mental deficiency (borderline defective, defective, and defect, type unclassified) the expected rate is 2.6%, not significantly higher than the rate of 1.6% in the full-term infants although in the same direction. Of the infants with a birth weight less than 1,501 gm., 50.9% have neurological or intellectual defect; some of these also have a major visual handicap. The adjusted percentage of premature infants who show some departure from normal development is 25.7%, compared to 12.8% of the full-term controls.

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Enzymes in Surgery.—Many of the physiological and pathological processes that the surgeon attempts to correct are motivated by enzymes. Their role has become more apparent as the chemistry and physiology of the diseases he treats have been studied. To mention a few examples: the deposition of fibrin and its solvation, the liquefaction of necrotic tissue, digestion and its disturbance, and the growth of tissues—all are brought about by the help of enzymes. When, for example, the surgeon removes the pancreas or most, if not the entire, stomach or colon, the missing enzymes must be compensated for by some means. Furthermore, certain diseases like peptic ulcer, ulcerative colitis, regional enteritis, pancreatitis, and many other diseases must be related to, if not caused by, disturbances in enzymatic activity. These diseases could be more intelligently dealt with if the distortion of the enzyme pattern were known. Parenthetically, the catgut the surgeon uses is "absorbed" through the action of enzymes. With the background in mind, the surgeon has added enzymes from an external source to pathophysiological processes in the hope that their evolution may be brought about more rapidly or completely. By this method he has attempted to aid inflammation, thrombosis, the resolution of infection and healing. The treatment of burns and empyemas has been attempted. Anyone who has had the experience of seeing large amounts of burn slough quickly, removed by the use of enzymes after two days, the bedsore converted to a clean granulating lesion in two or three days, necrotic slough removed from an x-ray burn, or the pus of the empyema cavity quickly liquefy and drain cannot help but be impressed that enzymes provide powerful adjunct help for the surgeon. On the other hand, when the lesion is not helped by the application of enzymes, the surgeon does not seem to understand that the naturally occurring enzymes have not worked, hence the lesion; that conditions were not or could not be established to allow the externally applied enzymes to work; or that the enzymes were asked to do an impossible task. For example, no enzyme has yet been discovered that will aid the separation of necrotic bone or to dissolve "leatherized" human skin.—E. L. Howes, M.D., Use of Enzymes in Surgery, *The Surgical Clinics of North America*, April, 1956.

LONG-TERM FOLLOW-UP OF PATIENTS WHO RECEIVED 10,098 SPINAL ANESTHETICS

SYNDROME OF DECREASED INTRACRANIAL PRESSURE (HEADACHE AND OCULAR AND AUDITORY DIFFICULTIES)

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• The headache that frequently follows spinal anesthesia is sometimes associated with visual and auditory difficulties and dizziness. This syndrome was studied in connection with 9,277 anesthetizations by the spinal technique, and the data were compared with those from 1,000 other patients who were given general anesthesia over the same period of time.

The over-all incidence of the headache, which occurred in 9,277 anesthetizations, was 1,011, or 11%. The oldest patients were least susceptible to it, and men were less susceptible than women. Its incidence when needles of small diameter were used was much less than that with needles of large diameter; the 22-gauge needle was found best for routine use. Headache could be virtually eliminated by the employment of a 24-gauge needle. The data on duration and time of onset of the headache, on the effects of postural changes, and on the visual and auditory phenomena indicate that this syndrome results from a decrease in cerebrospinal fluid pressure and that the decrease is caused by leakage of the fluid.

Patients' mental reactions to the suggestion that they be given spinal anesthesia have been frequently unsatisfactory. This feeling has been shared by a significant segment of the medical profession. These attitudes have been conditioned by several aspects of this method of anesthesia. In the first place there is a desire on the patient's part not to be awake during an operation. He also worries that the anesthetic might "wear off." Secondly, either through past experience or through accounts of others, the patient knows that headache, backache, or paralysis may follow spinal anesthesia. These objections to an otherwise good method of anesthesia might be accepted and spinal anesthesia abandoned entirely if substitute methods provided the same excellent operating conditions and a greater freedom from mortality. The introduction of curare and synthetic myoneural-blocking agents seemed at first to solve the problem of obtaining the muscular relaxation hitherto obtained with spinal or deep general anesthesia. This relaxation has been obtained not without a price, for there may be an increased mortality associated with the use of at least some of the relaxant agents.[1] Similarly, deeper levels of general anesthesia may call forth hypotension on a direct myocardial depressant basis,[2] adverse effects on renal and hepatic blood flow,[3] and a higher postoperative morbidity.[4]

When one analyzes the disadvantages of spinal anesthesia the neurological sequelae loom large. The fact that a patient wants to be unconscious or fears incomplete pain relief during an operation can easily be countered by a little bit of the art of anesthesiology. But what of neurological disease? In a large-scale study of this problem by us,[5] it was found that neurological disease need not follow spinal anesthesia if a proper technique of administration is employed. The most gratifying result was the failure to discover persistent, progressive major neurological disease. Minor sequelae were found and their incidence and peculiar characteristics described.[6] Now we believe that the matter of headache must be placed in its proper perspective. Fortunately, from the lay viewpoint, it is not well known that headache is frequently accompanied by ocular and auditory difficulties as well as dizziness. We choose to call this group of symptoms the syndrome of decreased intracranial pressure, a term suggested by Page.[7] The present paper will show that the incidence is high with some techniques of spinal anesthesia but that the syndrome is largely preventable if the proper precautions are taken.

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Material

During the years 1948-1951, at the Hospital of the University of Pennsylvania, we observed 8,460 patients who had received a total of 10,098 spinal anesthetics for all types of surgical procedures performed below the diaphragm. Eight hundred twenty-one anesthetizations had been done at other institutions prior to admission, so that in this report data on 9,277 anesthetizations will be analyzed. The patients fell into all categories of anesthetic risk and were carefully selected to avoid aggravation of preexisting neurological disease. A uniform, meticulous technique was employed but with deliberate variation of lumbar puncture needle size, of anesthetic drugs, and of methods commonly used to prolong spinal anesthesia. Every detail of the anesthetic administration was recorded. The patients were not only followed in the immediate postoperative period to elicit possible sequelae but were contacted in writing, interviewed, or examined from six months to five years later to discover delayed, persistent, or progressive disease. In this way information about 89% of the total number of anesthetics was obtained for at least a six-month period.

To determine if neurological sequelae were specific for spinal anesthesia we followed 1,000 patients given general anesthesia over the same period of time. The method of study, the age groups involved, and the types of operation performed approximated those in the series of pa-

tients given spinal anesthesia. The percentage of individuals given general anesthesia from whom information became available in the postoperative period approached that of the group who received spinal anesthesia. Obviously this method of study sensitized our patients to the possibility of development of disease. Whether the patients had received spinal anesthetics or were part of the control series of persons who had received general anesthetics, interesting comments were received. A middle-aged woman wrote, ". . . the only thing that had an effect on me was the gas . . . and ether dried the scalp and it felt so tight and drawn and my hair came out." Nevertheless, it was thought worthwhile to uncover the information we were seeking.

Results

Triad of Headache and Ocular and Auditory Difficulties.—The over-all incidence of headache and ocular and auditory complications from the 9,277 procedures was as follows: "spinal" headache, 1,011 patients (11.0%); ocular difficulties, 34 (0.4%); and auditory difficulties, 35 (0.4%). The headaches we report here had certain special features. They were postural in nature, appearing with the assumption of the erect position and usually relieved by recumbency. The location of the headache was frontal, occipital, vertex, or nuchal, or in combinations of areas, probably depending on the particular intracranial pain-sensitive structure stimulated. The severity, duration, and time of onset of the headache varied. Descriptive terms used by our patients included: constricting band, heaviness, vacuum-like, dead weight, "lead weight," "worse on moving," and "makes sounds echo." Occipital headache, nuchal pain, and stiff neck were not construed to be signs of meningitis or of meningismus, for accompanying evidences of fever or of inflammatory cells in the cerebrospinal fluid were not found. Rather, spasm and pain in the neck muscles could be interpreted as a reaction to pain similar to that in other areas of the body. Stiff neck and tender areas in the neck muscles are common accompaniments of headache no matter what the cause. Headaches were also found in the control series of 1,000 patients given general anesthesia, but they were of a nonspecific nature.

The ocular difficulties reported were double vision, blurring, "trouble in focusing," spots before the eyes, photophobia, scintillation, and "trouble in reading." The auditory complaints included: decreased hearing, "affected" hearing, obstruction, plugging, "popping," tinnitus, buzzing, and roaring. Few of these symptoms were found in the series of patients receiving general anesthesia alone; when they were found they were related to a patient's preexisting medical disease. The symptoms we have enumerated can be definitely related to lumbar puncture rather than to the introduction of the spinal anesthetic. In controlled series of lumbar punctures in our hands, and in those of others,[8] this same group of symptoms was found.

Whenever the opportunity arose to perform a second lumbar puncture after the onset of spinal anesthetic headache, for diagnostic or therapeutic reasons, the cerebrospinal fluid pressure was found to be negligible or absent. Although this is not an invariable finding in everyone's experience, the association has been close enough to indicate a cause-and-effect relationship. This, combined with bits of evidence to be discussed, has led us and others to ascribe headache and the associated symptoms to leakage of cerebrospinal fluid through a persistent dural fistula left by the lumbar puncture needle. When cerebrospinal fluid pressure is lowered, a compensatory intracranial vasodilation, aggravated by the erect position, which produces traction on the pain-sensitive dilated blood vessels, gives rise to a vascular type of headache. We never have been able to discover an increase in the cerebrospinal fluid pressure after spinal anesthesia. Thus it cannot be assumed that infection or cerebrospinal fluid hypertension plays a role in the development of the usual headache after spinal anesthesia.

Nature of "Spinal" Headache.—The over-all incidence of headache in our series was 11%. This may be compared with the 18% found by Thorsen [8] in 50,000 cases from various sources. Occurrence of headache according to age of the patient is shown in table 1. The incidence of headache decreased after the fifth decade, with the greatest frequency found in the third and fourth decades. This is a phenomenon observed by others. In part this difference among age groups may be attributed to an elevation of pain threshold in the aged, perhaps to a progressive decrease in sensory neural elements with increasing age. There is a known decrease in vibratory sensibility in the aged.[9] There may also be a decrease in elasticity of the cerebral vessels with aging. The age factor in headache cannot be ascribed to earlier ambulation in the young or to a greater fluid replacement parenterally in one group as compared to the other. The latter by increasing the cerebrospinal fluid pressure tends to mitigate both the number and severity of headaches. If anything, the older patients received fluids with greater caution and were out of bed just as early, to avoid postoperative surgical complications. A 10% incidence of headache in the second decade suggests that entirely different influences may bear on this complication in the very young. However, the finding may have no statistical significance.

TABLE 1.—*Relation of Age of Patient to Incidence of "Spinal" Headache*

Age, Yr.	Spinal Anesthetics, No.	"Spinal" Headaches No.	"Spinal" Headaches %
10-19	537	51	10
20-29	1,994	321	16
30-39	1,833	261	14
40-49	1,759	192	11
50-59	1,736	133	8
60-69	1,094	45	4
70-79	297	7	2
80-89	27	1	3
	9,277	1,011	11

Incidence According to Sex: The incidence of headache analyzed according to sex was as follows: 302 "spinal" headaches (7%) in 4,063 anesthetizations in men and 709 headaches (14%) in 5,214 anesthetizations in women. Here the over-all percentage in women was almost twice as high as that in men. Again this is a phenomenon observed by others. The main reason for the striking sex difference is the inclusion of obstetric cases in the female group. Table 2 confirms this conten-

tion, for it can be seen that headache followed vaginal delivery with the patient under spinal anesthesia with a frequency of 22%, twice the over-all figure in the series at large. The reasons for this may be the extreme changes in intra-abdominal pressure during labor, which could influence cerebrospinal fluid pressure; the rapid changes in blood volume following delivery; the dehydration during labor; and the lesser attention paid to fluid replacement parenterally after delivery. If the obstetric cases are

TABLE 2.—*Incidence of "Spinal" Headache After Spinal Anesthesia Administered for Vaginal Delivery*

Age, Yr.	Patients Receiving Spinal Anesthesia for Delivery, No.	"Spinal" Headaches No.	"Spinal" Headaches %
10-19	52	5	10
20-29	682	157	23
30-39	244	58	24
40-49	10	1	10
	988	221	22

removed from consideration, headache still proved to be more of a problem in women: 302 "spinal" headaches (7%) in 4,063 anesthetizations in men and 489 headaches (12%) in 4,276 anesthetizations in women. It is difficult to relate this to a constitutional variation between men and women in regard to pain perception or susceptibility. The role of the psyche in the development of headache in either sex seems negligible. To prove this point we gave spinal anesthetics to 100 persons anesthetized first with general anesthetics. Although none of these people knew that spinal anesthetics had been administered, the percentage occurrence of typical postural headache was the same as in the series at large.

Relation of Technique and Size of Needle: In an earlier communication,[10] we pointed out that the most important aspect of the sequelae to lumbar puncture and to spinal anesthesia was the trauma induced by the needle. Table 3, wherein the diameter of the lumbar puncture needle is related to headache, confirms our earlier observations. In the first paper of this series [8] errors appeared in the percentage column of table 6. A correction was printed later.[11] It can be seen that the incidence of headache decreased progressively with smaller needle diameters. There was not only a lesser occurrence of headache but less severity and duration. The employment of a 26-gauge needle for lumbar puncture, with deliberate hydration, can make headache a negligible complication after spinal anesthesia.[12] In our series a 16-gauge needle was employed for the introduction of a ureteral-type of catheter to produce continuous spinal anesthesia. Not only were the technical difficulties greater [13] but the incidence and severity of headache and ocular complaints were so prohibitive that we soon restricted this technique to the older age groups, wherein headache was not as much of a factor, or the method was reserved for those situations in which the greater safety and better control with the continuous technique were a major consideration. For routine use and freedom from technical difficulty, a 22-gauge needle proved to be best. The over-all incidence of headache with this needle was nearly 9%, but the headaches were generally mild.

Convincing evidence that lumbar puncture headache results from leakage of fluid through a fistula left by the needle with a consequent decrease in cerebrospinal fluid pressure comes from data of the kind presented in table 3. Perhaps because of lack of vascularity the dura does not heal readily. Leakage through a needle opening has been seen at subsequent laminectomy and at postmortem examination after prior lumbar puncture. Such fistulas can be found as long as 14 days later. In experiments in humans, Wolff [14] has produced headache regularly by lumbar puncture and drainage of 20 cc. of cerebrospinal fluid with the subject in the erect position. This drainage type of headache could readily be relieved by artificially raising the cerebrospinal pressure with injected saline solution. When headache does not follow spinal anesthesia, even if large-gauge needles are employed, a possible explanation is that the underlying arachnoidal membrane may have prolapsed to occlude the dural opening and thereby prevent leakage. This, too, has been seen at laminectomy. Because fistulas seem to be produced so easily, various techniques of lumbar puncture and specially pointed needles have been devised. We believe that an oblique insertion of the needle to puncture the dura and arachnoid at different levels, and favor prolapse of arachnoid, cannot be done deliberately or consistently. Likewise, it has been suggested that the bevel of the needle be inserted parallel to the longitudinal fibers of the dura so that the fibers are spread rather than sectioned. In a series of 100 cases of spinal anesthesia in which the bevel of the lumbar puncture needle was inserted in a parallel position, we found headaches slightly fewer in number but not significantly different from the entire series.

In summary of this phase of spinal anesthesia, it can be said that headache need not follow anesthesia if a careful technique and fine needles are employed. One can employ prophylaxis. If headaches do occur, treatment can logically be directed at the pain sources within the cranium with pharmacological agents, or therapy can be directed toward increasing cerebrospinal fluid pressure. Increased bodily hydration or the application of a tight abdominal binder will sometimes relieve the milder headache. A second lumbar puncture with replacement of

TABLE 3.—*Relation of Gauge of Needle Used for Lumbar Puncture to Incidence of "Spinal" Headache*

Needle Gauge	Spinal Anesthetics, No.	"Spinal" Headaches No.	"Spinal" Headaches %
16	839	151	18
19	154	16	10
20	2,698	377	14
22	4,952	430	9
24	634	37	6
	9,277	1,011	11

fluid will alleviate headache immediately. The reasons are not clear, but sometimes relief will be permanent after this maneuver, despite the fact that the dura has been punctured a second time. Neither is the mechanism clear whereby the epidural placement of fluid is said to relieve headache. It may be due to a cushioning effect on the dural column of fluid. There is evidence that some of the epidural fluid traverses the fistula to raise cerebrospinal fluid pressure directly. Another possibility is the

production of a reparative reaction in the epidural tissues, enough to close the opening. A word of caution must be added against the practice of injecting solutions indiscriminately into the subarachnoid space to relieve headache. Whenever a foreign substance is added to the cerebrospinal fluid there is the hazard of meningitis or arachnoiditis. We have heard of signs of irritation in the cauda equina after the epidural placement of saline solution. Direct artificial elevation of the cerebrospinal fluid pressure should be reserved for the treatment of incapacitating headaches when nausea, vomiting, or dizziness are protracted and when an ocular nerve palsy seems imminent (see below).

Relation of Type of Anesthetic Agent: In table 4 it can be seen that the particular local anesthetic agent employed for spinal anesthesia bore no relation to the number of headaches found. The apparently higher incidence in the miscellaneous group is attributable to the fact that piridocaine (Lucaine) was used for anesthesia during vaginal delivery in 45 patients. One cannot draw the conclusion from these figures that one agent is less of an irritant than the other. We have suggested that the pain source is intracranial in origin. Since significant concentrations of local anesthetics do not circulate into the intracranial portions of the cerebrospinal fluid space, this is indirect evidence for the concept that headaches do not eventuate from irritation or infection.

TABLE 4.—*Relation of Drug Used for Spinal Anesthesia to Incidence of Headache*

	Spinal Anesthetics, No.	"Spinal" Headaches	
		No.	%
Tetracaine (Pontocaine)	7,127	780	11
Procaine	1,399	146	10
Dibucaine (Nupercaine)	485	49	10
Procaine-tetracaine	164	18	11
Miscellaneous (piridocaine [Lucaine], Pyrrolocaine [β-pyrrolidinoethyl *p*-n-propoxybenzoate])	102	18	16
Total	9,277	1,011	11

Onset and Duration: The onset of post-lumbar-puncture or spinal headache took place soon after the assumption of a head-up position. In this series the practice of so-called early ambulation of surgical patients was followed as frequently as possible. Headache appeared in some cases when the patient first lifted his body in bed or when he got out of bed for the first time. If the headaches were severe, most patients soon learned the value of recumbency in relieving their symptoms. The data in table 5 indicate the time of onset of headache after anesthesia. The fact that headache appeared after several days or even weeks explains why in some reported series the incidence of headache is exceptionally low when compared to data such as ours or Thorsen's.[8] The patients had simply not been followed long enough in the postoperative period to detect the true incidence. The same criticism may be leveled at reported series of cases wherein the number of headaches have been ascertained after diagnostic lumbar puncture. Usually the headaches found are few, but, when careful follow-ups are done, the true facts emerge.[15] In our own series the appearance of headache sometimes was reported to us long after the patient had left the hospital. Just why headache should be delayed in onset is not easy to explain. One can postulate slow leakage of cerebrospinal fluid through a fistula until such time as loss of fluid overbalances production or until a specific pain threshold is reached.

For many years it has been the custom to require patients to remain flat in bed for arbitrary periods of time after spinal anesthesia to prevent or minimize headache.

TABLE 5.—*Time of Onset of "Spinal" Headache in Postoperative Period*

Days After Operation	"Spinal" Headaches	
	No.	%
Day of operation	89	9
1	302	29
2	216	21
3	123	13
4-6	115	11
7-12	12	1
1 mo	2	0.2
5 mo	2	0.2
No data	150	15
	1,011	

We have no evidence that this is a rational practice. The custom may have been perpetuated simply because headaches appeared at a later time. Leakage of cerebrospinal fluid probably takes place during the operation and afterward even with the patient recumbent. A recent communication also suggests that there is no value to this long-established custom.[16]

A surprising fact about lumbar-puncture headache is its duration in certain cases. Time and time again people have written us to describe headaches of long duration. The duration of headaches in the reported series, when data were available, may be seen in table 6. The range was from one day to 12 months, with 53% of the patients with headache ceasing to complain after four days. It is hard to conceive of persistent fistulas, leakage, and decreased cerebrospinal fluid pressures for these long periods of time. Yet, when examinations have been made, a decreased pressure has occasionally been found.[8] Some of the complaints we received were intriguing. The mother of a 12-year-old boy given spinal anesthesia for an appendectomy reported six months later that her child had had headache at least four times weekly and had been unable to use a swing in the backyard because of dizziness. For almost a year a middle-aged woman was

TABLE 6.—*Duration of "Spinal" Headache*

Duration, Days	"Spinal" Headaches	
	No.	%
1-2	245	24
3-4	296	29
5-7	193	19
8-14	79	8
3-6 wk	49	5
3-6 mo	19	2
7-12 mo	38	4
No data	92	9
	1,011	

unable to stand erect without developing headache. There must be several explanations for these phenomena. It is probable that the complaints had a true organic basis in some cases. Torda,[17] in order to explain persistence of headache after a migrainous attack, postulated a change in cerebral blood vessel walls of an edematous and, later, fibrous nature. Experimental evidence for this was obtained by perfusing blood vessels with acetylcholine. Some of the long-lasting headaches after spinal anesthesia may have had their origin in a similar vascular change. To explain other headaches of long duration one can envisage a headache initiated at first by cerebrospinal fluid drainage and then perpetuated in the individual's psyche by the stress and strains of everyday life. The source of the headache is no longer changes in intracranial pressure but painful areas in muscle caused by prolonged attitudes of tension. In this respect, when headache is viewed in general, tension and anxiety are often the underlying etiological factors.

Nature of Ocular Difficulties.—In our follow-up of patients after spinal anesthesia, we encountered 34 individuals who had difficulty with vision. The descriptive complaints provided by these people ran the gamut of double vision, blurring, inability to read, sensitivity to light, spots before the eyes, and trouble in focusing. One man wrote, "I have never been able to drive a car since operation because I do not have normal vision." On investigation this man proved to have terminal uremia. A young woman wrote, "My first time on the street after operation the air seemed alive with silvery streaks and black spots. These have continued to be present." On thorough ophthalmic examination abnormalities were not discovered, and she was relieved of apprehension. However, most ocular complaints were genuine.

In all but eight cases the visual trouble arose in association with typical postural headaches. Interesting was our discovery of three proved cases of lateral rectus muscle paralysis, and the symptom of prolonged double vision in three other persons suggested that paralysis might also have been present. These six cases followed the use of a 16-gauge needle for continuous spinal anesthesia given through a catheter. Five of the six patients had severe headaches, in three localized to the occipital area. One cannot help but relate the palsies and the other ocular complaints to headache and consequently to a decrease in intracranial cerebrospinal fluid pressure. The ocular nerve palsies, in our experience, came on rather suddenly a week or so after operation and persisted from a few weeks to six months. In every case there was complete functional restitution of vision. It must be assumed that an ocular nerve palsy represents an end-stage of whatever ocular abnormality is present. Therefore, more benign ocular complaints may represent phases or steps toward the final result without progression. There have been many reported cases of cranial nerve palsy arising after spinal anesthesia, but the abducens nerve usually has been involved.[8] One theory of origin has been that, with brain displacement and traction on supporting structures, a motor nerve, particularly one with a long intracranial course, could be paralyzed by pressure against osseous structures, or, in the passage of the nerve through the cavernous sinus, excessive venous dilatation might produce the same effect. Either of these ideas seems logical, and what better substantiation for the theory of decreased intracranial pressure could one ask?

As a result of encountering these nerve palsies, we have tried to avoid using large-gauge needles and continuous spinal anesthesia given through a catheter except in the older patients, where headache is not expected. If confronted with intractable and severe headache in our patients, we have resorted to all available means of increasing cerebrospinal fluid pressure to avoid the possible development of a cranial nerve palsy. However, the best approach is that of prophylaxis and the employment of a small-gauge lumbar puncture needle.

Nature of Auditory Difficulties.—Thirty-five of our patients described hearing difficulties. In many there was associated dizziness, but since this is a difficult symptom to evaluate we have chosen to confine our discussion to auditory problems. Our attitude is the same toward the symptom of nausea, which was a complaint of many people. In Thorsen's series,[8] dizziness was found in 9.1% of the cases. Thorsen could not decide if this symptom was of otogenous or cerebellar origin. Dizziness, nausea, and hearing difficulties were found in our control series of general anesthetics but could be ascribed usually to a patient's underlying medical disease. For example, an elderly man had dizziness and severe headaches after general anesthesia, but he had advanced hypertension as well. After spinal anesthesia people complained of buzzing, popping, and clogging of the ears, of loss of hearing, humming, roaring, and stuffiness. A 62-year-old woman wrote, "I feel spinal has affected my hearing which I understand it does with quite a few people." Another reported, "I lost my hearing after operation—it could have been caused by the anesthesia."

What significance can we attribute to these symptoms? An analysis of accompanying symptoms again reveals that with few exceptions hearing troubles were associated with typical postural headaches. Hence a decrease in cerebrospinal fluid pressure must be implicated once more. That there is an anatomic communication between the subarachnoid space and the cochlea is well known. Experimental work by Hughson[18] demonstrated that with a decrease in cerebrospinal fluid pressure there was a fall in intralabyrinthine pressure followed by a functional inability of the ear to transmit high tones. We have seen on several occasions restitution of an audiogram to normal values when cerebrospinal fluid pressures were artificially elevated toward normal in individuals with headache and decreased hearing after spinal anesthesia. One might assume that, in addition to deafness, the other auditory complaints after spinal anesthesia might be secondary to a decreased cerebrospinal fluid pressure. As in the case of headache and ocular difficulties, auditory abnormalities may be prevented by a proper technique of lumbar puncture.

Comment

In a study of 10,098 spinal anesthetics, appreciable numbers of patients were discovered who developed typical lumbar puncture headaches accompanied in some

instances by difficulty in seeing and hearing. An inquiry into the factors responsible for these phenomena was made. The data that we have presented confirm the observations and clinical experiments made by many others during the relatively long history of the study of spinal anesthetic problems. In analyzing our material and reviewing the extensive writings on the subject, we have shown that the afore-mentiond symptoms can be high in incidence, troublesome, and indeed occasionally incapacitating for patients. The study of neurological sequelae of spinal anesthesia in which we have been engaged has been designed to delineate the specific factors leading to these sequelae, to point out the now well-established prophylactic measures, and to suggest the best therapeutic procedures to adopt if trouble arises. Only with information of this sort do we feel that there is justification in continuing the use of spinal anesthesia.

The evidence is conclusive, we believe, that headache and associated symptoms arising after spinal anesthesia are symptomatic of a decrease in cerebrospinal fluid pressure. The conclusion also seems inescapable that leakage of spinal fluid leads to this change in pressure. The clinical manifestations of this change are seen as a result of an effect on intracranial blood vessels and nerves. For this reason we concur in labeling the triad of symptoms—headache and ocular and auditory difficulties—the syndrome of decreased intracranial pressure. The evidence from which this syndrome gains acceptance is partly circumstantial and partly experimental. It is obvious that one could not hope to demonstrate a lowered intracranial pressure in every case, for the modifying factors in any one instance can be many and the physiological alterations may be relatively slight to produce the ultimate symptoms. Primarily, what we have shown is that there is a striking amelioration of undesirable symptoms as the trauma of lumbar puncture is eliminated. In our hands and those of others, sequelae of lumbar puncture have been brought near to the vanishing point by the employment of careful techniques. After consideration of the lumbar puncture itself, the chief modifying factors in the appearance of symptoms have been the age and sex of our patients, with pregnancy a major influence in females. Bodily hydration as it pertains to the production of cerebrospinal fluid is also a factor. The local anesthetic employed for spinal anesthesia does not affect the appearance of symptoms. Although the type of study we chose to demonstrate these facts sensitized our patients to the possibility of ensuing trouble, psychological attitudes bore no influence on the number of genuine complaints found.

The seriousness of the complications of spinal anesthesia is illustrated by the fact that headaches may be totally incapacitating and that they may persist for months after anesthesia. An accompaniment of severe headache may be paralysis of one of the extraocular muscles, which we discovered in six of our patients. Finally, deafness, although temporary, was a real complaint of a number of patients. We summarize these findings only to point out that they can be avoided and that spinal anesthetics must be administered with the least anatomic and physiological disturbance to the patient.

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Fluoridation of Water.—With regard to acute fluoride poisoning there is at least a 2,500-fold factor of safety in water fluoridation. The mechanics of water fluoridation are such that it is impossible to produce acute fluoride poisoning either by accident or intent. Crippling fluorosis, characterized by a stiffening in the back due to caicification of the broad ligaments of the back, occurs with a daily intake of 20 to 80 milligrams of fluoride or more for 10 to 20 years. Since five gallons of fluoridated water at 1 ppm F contain 20 milligrams, it is obvious that crippling fluorosis can never be produced by drinking fluoridated water. The earliest evidence of osteosclerosis, a hypercalcification detectable by roentgen examination, does not occur with an intake of fluoride below eight to 10 times the level of fluoridated water. . . . The evidence with respect to heart disease, kidney disease, cancer, and possible influence of fluoride on the thyroid . . . indicate(s) no influence of fluoride intake on any of these at the levels found in any water supplies in the United States. Studies on experimental animals with the use of radioactive fluoride show that the thyroid gland does not concentrate fluoride as it does iodide. The presence of renal impairment in experimental animals and in human beings with long-standing kidney disease appears not to affect excretion of fluoride by the kidneys. The comprehensive analysis of the Newburgh-Kingston Caries-Fluorine Study after 10 years of experience, added to the wealth of evidence previously reported, demonstrates conclusively two important facts —fluoridation is effective in reducing dental caries and it is a safe public health practice.—D. B. Ast, D.D.S., M.P.H., and E. R. Schlesinger, M.D., M.P.H., The Conclusion of a Ten-Year Study of Water Fluoridation, *American Journal of Public Health*, March, 1956.

PALATINE PETECHIAE, AN EARLY SIGN IN INFECTIOUS MONONUCLEOSIS

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• In 21 of 38 cases of proved and one case of probable infectious mononucleosis petechial eruption on the soft palate was observed. The eruption consisted of multiple pin-point lesions on the soft palate, usually near the junction with the hard palate but sometimes near the midline more posteriorly. In one patient the petechiae were also noted on the uvula. The number varied from 10 to several hundred. They appeared from 3 days to two weeks after the onset of symptoms, lasted from 3 to 11 days, and then faded, leaving no trace. In two cases in which platelet counts, capillary fragility tests, and clot retraction tests were done, there was no sign of a hemorrhagic diathesis. This eruption was primarily responsible for an early, correct diagnosis of infectious mononucleosis in two instances.

The syndrome of infectious mononucleosis has intrigued clinicians since 1889, when Emil Pfeiffer first described what he called glandular fever.[1] Repeated attempts to isolate the etiological agent have since failed, and today we are still very much in the dark as to whether this is really a disease or a syndrome. As in all idiopathic diseases, certain diagnostic criteria are essential for uniformity in appraising its clinical features. This was lacking until 1922, when Longcope [2] first described the atypical cells, and 1923, when Downey and McKinlay [3] gave a more accurate description of them. This enabled clinicians to more adequately explore the clinical features of the disease. In 1931, Epstein and Dameshek [4] in the United States and Johansen [5] abroad first described neurological involvement in this disease. In 1932 when Paul and Bunnell [6] demonstrated the heterophil antibodies, the way was cleared for clinicians everywhere to accurately explore the clinical features of infectious mononucleosis, and since that time the literature has been studded with reports that have exposed infectious mononucleosis as one of the most protean diseases. Indeed, its diverse manifestations include such features as serous meningitis, encephalomyelitis, neuritis, virus encephalomyelitis (Guillain-Barré syndrome), cerebellar dysfunction, optic neuritis, retrobulbar neuritis,[7] benign interstitial nephritis with albuminuria, a virus-like pneumonia, myocardial involvement, hypoplastic and hemolytic anemias, thrombocytopenic purpura,[8] hilar adenopathy,[9] hepatitis, and splenic rupture. Practically no organ or system has escaped involvement by this disease.

Early in 1955, we began to notice the frequent occurrence of stippled petechial hemorrhages in the soft palate in patients with infectious mononucleosis. In May, 1955, we began to collect a series of consecutive case records and since have collected a total of 20 cases of mononucleosis, in 10 of which patients displayed this petechial eruption. In some cases, the diagnosis was suspected primarily because of the eruption, and in others it was a helpful sign. For this reason, it is felt the following report may be of some clinical interest.

Clinical Material

The 20 patients were all males between the ages of 18 and 32 years. Diagnoses in all but one were confirmed by hematological and serologic methods including guinea pig kidney absorption and beef erythrocyte absorption tests. The eruption consisted of multiple, pin-point petechiae on the soft palate, usually near the junction with the hard palate but sometimes located near the midline more posteriorly on the soft palate. Sometimes sparse petechiae were seen on the hard palate also, but usually they were confined to the soft palate. In one patient some petechiae were also noted on the uvula. In no case were there associated petechiae on the skin or in other parts of the oral cavity. The number of petechiae varied from 10 to several hundred, and the usual distribution and appearance is shown in the figure, which is an actual photograph of the lesion in one patient. This eruption was seen in 10 of 20 consecutive patients and was noted from three days to two weeks after the onset of symptoms in all cases. It lasted from 3 to 11 days and then faded, leaving no trace of its presence. Only one patient had an associated maculopapular skin eruption when seen by us. In two patients with petechiae, platelet count, clot retraction, and capillary fragility tests were normal. In the others, tests were not done, but there was no reason to suspect a hemorrhagic diathesis.

Of the 10 patients who displayed the petechial eruption, 6 had typical mononucleosis in every respect and do not merit a detailed presentation here. Two of the cases will be presented because they illustrate the value of this sign in elucidating a diagnosis; in the third case, the patient manifested this eruption and a clinical impression of infectious mononucleosis was arrived at but was not confirmed by heterophil antibody tests. The fourth case illustrates an unusual manifestation of infectious mononucleosis.

Report of Cases

CASE 1.—An 18-year-old airman was admitted July 23, 1955, with a three-day history of sore throat, fever, malaise, and cervical adenopathy. He was first seen in the dispensary where physical examination revealed temperature of 101 F (38.3 C). The pharynx was fiery red and diffusely injected with scattered purulent exudates. There were numerous fine showers of petechiae in the soft palate. Tonsillar and cervical nodes were enlarged and tender. The spleen and liver were not palpable. Because of the finding of petechiae, a heterophil antibody test was made and showed a presumptive titer of 1:224, a titer of 1:112 after guinea pig kidney absorption, and no titer after beef-cell absorption. Abnormal thymol turbidity and cephalin flocculation tests were the only evidences of hepatic dysfunction. He was returned to duty asymptomatic after 12 days of rest. Clinically, this case was in no way unlike a typical streptococcic

pharyngitis when first seen, and it is doubtful if mononucleosis would have been strongly considered at this stage except for the presence of the petechial eruption.

CASE 2.—A 25-year-old airman was admitted Sept. 2, 1955. Nine days before, he had gone to a dispensary in Okinawa with epigastralgia and frontal headaches. Examination, including a stool specimen for ova and parasites, was nonrevealing and his temperature was 99.4 F (37.4 C). He was placed on symptomatic therapy consisting of acetylsalicylic acid, acetophenetidin, and caffeine (APC) capsules and phenobarbital elixir. Four days later, he was transferred to Japan, arriving on Aug. 31. The next day, he noted itching and a macular rash on the neck, shoulders, and face. He reported to sick call 24 hours later, and the rash was seen to be maculopapular and to involve the face, neck, arms, trunk, palms of the hands, and soles of the feet. He had been given a diagnosis of measles on three occasions in the past. He was not ill and did not show toxic reaction, and there was no significant adenopathy or hepatosplenomegaly. He was thought to have a drug eruption, and all medication was stopped and the patient advised to return in 24 hours. Next day, his rash was even more pronounced and further examination revealed a petechial eruption involving the soft palate near the junction with the hard palate. There were also some petechiae in the midline more posteriorly on the soft palate. There was still no adenopathy, toxic reaction, or splenomegaly. Because of the petechiae, a diagnosis of mononucleosis was suspected and subsequently confirmed by a heterophil antibody titer on Sept. 2 that showed a presumptive titer of 1:896, a titer of 1:448 after guinea pig kidney absorption, and a titer of 1:14 after beef-cell absorption. Cardiolipin flocculation test was negative. Abnormal thymol turbidity (16.8 units) was the only evidence of hepatic dysfunction. He had a white blood cell count of 16,750 per cubic millimeter, with 72% lymphocytes. Many were atypical. After three days, the rash and petechiae began to clear and in two additional days they were gone. He was returned to duty asymptomatic after 15 days in the hospital.

CASE 3.—A 21-year-old airman was admitted Aug. 10, 1955, with a history of malaise, somnolence, headache, anorexia, and dark urine of one week's duration. Twenty-four hours prior to admission he had noted a sore throat and a transient erythematous rash on his left forearm. Examination revealed a temperature of 102.6 F (39.2 C); large, soft cervical and axillary nodes; and palpable liver and spleen. Tonsils were large with purulent cryptic exudate, and the throat culture grew a hemolytic Micrococcus (Staphylococcus). Punctate petechiae were noted in the soft palate and on the uvula. These were noted again three days later but faded afterward. White blood cell count was 16,950 per cubic millimeter, with 63% lymphocytes, none considered to be atypical; a repeat count revealed 50% lymphocytes and a total count of 6,100 cells per cubic millimeter but no atypical forms. There was an abnormal thymol turbidity (13.0 units) and cephalin flocculation (4 plus in 24 hours) test. Presumptive heterophil titer on five occasions was never higher than 1:28, and on Sept. 15 a presumptive titer of 1:14 was completely absorbed by beef cells, but this remains the only case in which the diagnosis was not considered to be confirmed by laboratory methods. Treatment for five days with penicillin was not effective, and daily temperature spikes to 103 F (39.4 C) were noted. Treatment with erythromycin was concomitant with lysis of the fever and symptoms, and he was discharged 19 days after admission, hepatosplenomegaly having receded.

CASE 4.—A 19-year-old airman was admitted Sept. 3, 1955, because of fever, sore throat, malaise, and chilliness of two days' duration. He was seen in the dispensary with temperature of 103 F (39.4 C) and was admitted to the ward. He was noted to have tenderness in the left upper quadrant of the abdomen, mild pharyngitis, and cervical adenopathy. By Sept. 6 he had generalized adenopathy, purulent tonsillitis, hepatomegaly, splenomegaly, petechial eruptions on the soft palate, and a slight stiff neck thought to be due to painful adenopathy. Blood smear showed 70% lymphocytes and a presumptive heterophil titer of 1:56, with a 1:14 titer after guinea pig kidney absorption and no titer after beef-cell absorption. A repeat titer of 1:224, obtained two weeks later, was completely absorbed by beef erythrocytes. Because of persistence of fever and signs of toxic reaction, he was started on cortisone therapy Sept. 9, 1955, and this was continued through Sept. 14, 1955. He responded well and was apparently convalescing well. Abnormal thymol turbidity (16.7 units) and cephalin flocculation tests were the only evidences of hepatic dysfunction. He was afebrile from Sept. 9 to Sept. 21. On Sept. 19, he noted epistaxis and was cauterized with 10% solution of silver nitrate. On Sept. 21, his temperature began to spike to 103 F, and he noted recurrence of his former symptoms plus marked nuchal rigidity. Lumbar puncture revealed clear fluid under a pressure of 360 mm. of spinal fluid. There were 21 polymorphonuclear cells per cubic millimeter of spinal fluid, and the total protein was 61.5 mg. per 100 cc. Culture of spinal fluid was negative. Blood cultures were normal on four occasions except for the first one, which grew a Micrococcus (Staphylococcus) pyogenes var. albus and was never reduplicated. This was thought to be a contaminant. Daily temperature spikes to 105 F (40.6 C) continued, and on Sept. 16 he did not recognize some friends, though he was still rational. At this time it was noted he had a fine tremor of arms and tongue and a coarse intention tremor and muscle twitching associated with nystagmus. He had generalized muscle weakness and was unable to maintain a sitting posture, but there was no sensory loss. Two days later, he showed past pointing, adiadochokinesia, and continued intention tremor. On Sept. 22 and 23 he had severe epistaxes requiring packing, absorbable gelatin sponge (Gelfoam), and finally cauterization. Temperature spikes continued until Sept. 27, when they slowly declined. He is still hospitalized at the time of this writing. This represents a classic form of a disturbing picture of meningoencephalitis with late development of cerebellar dysfunction.[10]

Fine petechiae clustered near junction of soft and hard palate and more posteriorly close to midline.

Comment

Until we completed this study, we were unaware of any reference to petechial hemorrhages as herein described in cases of infectious mononucleosis. However, a more thorough search has revealed that this was reported once before by Holzel.[11] He reports 16 sporadic cases seen over a 12-year period and mentions the apparent specificity of this finding, though he is unable to assay its frequency. In two of his cases the diagnosis was made clinically but was not confirmed by heterophil studies. The remainder were proved cases and did not differ appreciably from our cases in clinical features. He refers to cases previously reported that were complicated

by thrombocytopenia (Finlayson, 1951; Goldbloom and Denton, 1948; Kilham and Steigman, 1942). In these, petechiae were not limited to the soft palate at its junction with the hard palate; they were associated with petechiae on other parts of the oral mucosa and, in most instances, the skin as well. He states that Muller (1950) mentions dark red spots on the soft palate in two cases. Read and Helwig (1945), in a review of 300 cases,[12] found 4 in which petechiae were noted in the oral cavity, but they are not further described. Leibowitz, in a review of over 377 articles on infectious mononucleosis,[13] does not mention this finding, and it is not described in several of the standard texts of medicine and hematology.[14]

The petechiae are readily visible when an adequate examination is made. During the period of this study, 12 patients with common cold, 19 with acute pharyngitis, 6 with primary atypical pneumonia, 18 with infectious hepatitis, 14 with bronchitis, and 24 with tonsillitis were observed in the hospital, and none of these displayed the petechiae. However, it was noted that dilated vessels similar to nevi sometimes occurred and, when prominent, may suggest petechiae on a cursory examination but can be distinguished from them with careful scrutiny. Also, we encountered two Negro patients in whom raised pigmented spots occurred on the soft palate, but these were easily differentiated from petechiae by their color, their raised appearance, and their persistence.

In our short series of 20 cases, the incidence of petechial exanthema was exactly 50%. It is possible the others were seen too late to catch the eruption, as it seems to be an early manifestation, having occurred from three days to two weeks after the onset of symptoms in all cases. The lesion persisted from 3 to 5 days as a rule; however in one case it was noted to last 11 days. In two cases in which platelet counts, capillary fragility tests, and clot retraction tests were done, there was no sign of a hemorrhagic diathesis.

The case of the patient with meningoencephalitis and cerebellar dysfunction associated with mononucleosis was reported for two reasons: first, because this is an unusual manifestation of infectious mononucleosis, and, second, because there was one such case in a series of 20 consecutive cases. It is only by aggregating case reports that are associated with a consecutive series of cases that we can begin to get an idea of the frequency of the various complications of the disease. It is possible that the increased number of case reports of neurological complications of infectious mononucleosis is due to a higher index of suspicion on the part of the clinicians and more widespread familiarity with the clinical features of the disease, which has been made possible by more accurate case reporting after the work of Paul and Bunnell in 1932.[6]

Conclusions

Twenty consecutive patients with infectious mononucleosis seen from May to September, 1955, at one Air Force hospital were observed for the finding of petechial eruption in the soft palate. Nineteen of these had proved cases of mononucleosis; in 10 of the 20 cases the patients had petechiae on the soft palate early in the course of the disease. No petechial eruption was seen in 12 patients with common cold, 19 with acute pharyngitis, 6 with primary atypical pneumonia, 18 with infectious hepatitis, 14 with bronchitis, and 24 with tonsillitis observed in the hospital during this study period. The eruption consists of multiple pin-point petechiae occurring on the soft palate usually near the junction with the hard palate, sometimes near the midline more posteriorly. They are to be differentiated from increased vascularity and from pigmented spots sometimes seen in normal Negroes. Also, a similar eruption may occur in a case of hemorrhagic diathesis but is usually associated with an eruption elsewhere. In two cases this eruption was primarily responsible for an early correct diagnosis. In this series there was one case of meningoencephalitis with cerebellar dysfunction due to infectious mononucleosis.

Addendum

Since the above article was written, 19 additional patients with infectious mononucleosis have been seen by us. Of these, 11 displayed the described petechial hemorrhages of the soft palate during the early course of the disease. All 11 had classical clinical cases that were also serologically proved by positive heterophil antibody agglutination studies (with use of both guinea pig kidney and beef erythrocyte absorption studies). In one case the patient did not have the petechial hemorrhages and also did not have a positive heterophil antibody titer, but otherwise the case was classic, both clinically and hematologically.

2211 Kimberly Dr., Augusta, Ga. (Captain Shiver).

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RESULTS OF MOBILIZATION OF FIXED STAPEDIAL FOOT PLATE IN OTOSCLEROTIC DEAFNESS

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• *Otosclerotic deafness, in which the foot plate of the stapes becomes rigid and obstructs sound from reaching the cochlea, can be treated by surgical mobilization of the foot plate. The operative approach is such as to expose the stapes and incus to direct vision with good illumination and magnification. The operation itself, which should be rehearsed on at least 50 fresh cadavers, involves the use of a special mobilizer whereby pressure can be applied to the stapes; an additional instrument may be used for dealing with adhesions about the ossicles or round window.*

The operation has been used in 211 cases, and the results have been assessed by pure tone audiometry, speech audiometry, and speech discrimination tests. Striking improvement has been demonstrated in many cases, and in some there has been dramatic improvement on the operating table. Improvement is limited by the extent of cochlear involvement. In moderate and profound otosclerotic deafness, the mobilization operation can restore useful aided or unaided hearing.

The ideal operation to restore hearing in otosclerotic deafness should be a simple one that preserves nature's own pathway of sound conduction via the intact and unaltered ossicular chain. In otosclerotic deafness, the foot plate of the stapes becomes rigid and obstructs sound from reaching the cochlea. In order to permit sound to reach the cochlea freely, as nature provided, the rigid foot plate should be converted into a mobile foot plate.

The new surgical technique described by me in 1952,[1] which restored hearing in otosclerotic deafness by mobilization of the fixed stapedial foot plate, seems to fit the above requirements. An analysis of the results of this technique in the first 211 consecutive cases of otosclerotic deafness between April, 1952, and August, 1954, was reported before the American Laryngological, Rhinological and Otological Society at its annual meeting on March 17, 1955.[2] The mobilization operation described herein has been used continuously to date.

Mobilization of the stapes is not new. Kessel (1876), Boucheron (1888), Miot (1890), and, in America, Blake, Jack, and Burnett (1891-1893) tried various methods to mobilize the fixed stapes. Siebenmann in 1900 stated that all operations on the stapes were useless and should be abandoned. All these men performed the operation through a myringotomy opening, which in the vast majority of instances did not give sufficient exposure or direct vision of the stapes for it to be manipulated safely. The present technique, which widely exposes the stapes and incus to direct vision, is readily accomplished not through a myringotomy but rather by lifting the entire lower half of the drum out of its sulcus and folding it upward upon itself like an apron. The structures in the tympanum are thus brought into direct view. Present-day illumination and magnification of the operative field allow greater precision in the performance of this delicate operation. The antibiotics now control the hazard of postoperative infection.

The operation is short (about 20 minutes) and the shock to the patient is nil. The patient is ambulatory, on full diet, and without vertigo and leaves the hospital the following morning. No bandage or postoperative treatments are necessary. Patients may swim, dive, golf, and drive in the wind as before. Hearing improvement and, in some cases, normal hearing have been maintained for periods up to 48 months at the time of writing. The first otosclerotic patient whose stapes was successfully mobilized in April, 1952, still has normal hearing.

Rosen Technique of Mobilization of Fixed Stapedial Foot Plate

Operation is performed, with use of local anesthesia, through an ordinary ear speculum in the external auditory canal, using the Zeiss-Cameron loupe. One to 2 cc. of a mixture of three parts 2% lidocaine (Xylocaine) hydrochloride and one part epinephrine solution (Adrenalin chloride) is injected subcutaneously into the skin of the posterior wall, roof, anterior wall, and floor at the junction of the cartilage and bone.

An incision is made through the skin over the bony canal wall 6 to 7 mm. external to the drum, beginning posterosuperiorly at the point of junction of Shrapnell's membrane and the pars tensa of the drum. (It is always best to begin the incision higher rather than lower.) The incision is carried downward along the posterior wall, floor, and anterior wall as far as the point where the pars tensa and Shrapnell's membrane meet anterosuperiorly with instrument no. 1 (fig. 1). The skin is separated from the bone as far as the edge of the drum with instruments no. 2 and 3, starting the separation at the beginning of the incision. From this point of entry into the tympanum, the drum is progressively lifted out of its sulcus and reflected upward upon itself like an apron, with instrument no. 4.

In over 85% of the cases, portions of the incudostapedial joint are at once seen. The stapes, however, cannot be seen sufficiently to allow safe manipulation; therefore, about 2 to 3 mm. of the very edge of the posterior bony canal just external to the incus and stapes must be removed with instrument no. 5 in order to get a full view of the long process of the incus, the incudostapedial junction, the head, neck, sometimes the crura and the foot plate of the stapes, facial canal, the entire length of the stapedius tendon, chorda tympani nerve, a portion of the incudomalleolar articulation, and the inner aspect of the hammer handle.

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Read before the third Turkish Oto-Rhino-Laryngological Congress, Istanbul, Turkey, Sept. 2-5, 1955.

To test for mobility of the foot plate of the stapes, a finely pointed probe (instrument no. 6, fig. 1) is placed against the long process of the incus close to its articulation with the stapes and moved gently downward for a distance of about 0.5 mm. (fig. 2). When the normal foot plate of the stapes is freely movable in the oval window, the gentlest pressure of the probe against the long process of the incus causes free and unimpeded movement of the incus, incudostapedial joint, head, neck, and crura of the stapes, and stapedial tendon. The tendon of the stapedius is the structure to watch at all times, since its movement is the reflection of the foot plate movement. The foot plate of the stapes moves invariably whenever the head and crura move, and, when this happens, the tendon invariably moves in proportion to the movement of the stapes.

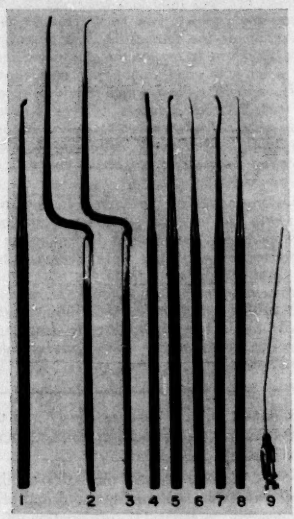

Fig. 1.—Instruments numbered in the order in which they are used in mobilization: 1, knife; 2, wide skin elevator; 3, narrow skin elevator; 4, separator; 5, curet; 6, explorer (curved); 7, mobilizer; 8, explorer (angulated); and 9, cut-off spinal needle used for suction.

These structures all can be seen to move together as one. The operator also can feel these structures moving. This associated sight and feel must be experienced often to master the technique. When the stapes is partially or incompletely fixed, it takes greater pressure of the probe against the long process of the incus to move the above structures even slightly, as measured again by the degree that the tendon can be seen to shorten and lengthen. Again, these structures can be seen to move together as one, however minutely; but when the foot plate of the stapes is completely fixed, very firm pressure of the probe against the long process of the incus causes the incus alone to move, but there is no movement whatever of the head, crura, foot plate, or tendon of the stapes.

When the stapes is rigidly fixed (stapes removed from cadavers and fixed in cement offer good practice to get the feel of the otosclerotic rigid stapes), variable pressure downward against the neck (only the neck, because it is the thickest and strongest part of the stapes) may suddenly loosen the foot plate with immediate improvement in hearing. For this purpose a specially curved, narrow mobilizer was devised (instrument no. 7, fig. 1). The palpating edge of the mobilizer is first inserted over the incudostapedial joint and is carried inward until one can feel the anterior crus of the stapes close to the foot plate. The instrument is pulled gently upward and outward hugging the anterior crus until one suddenly feels a dent or depression, which is the neck of the stapes. At this point the stapes withstands the greatest pressure without fracture of the crura (fig. 3).

Pressure downward in the line of the stapedial tendon is made until the stapes is mobilized. The direction of the stapedial tendon roughly follows the same direction as the crura and the long axis of the foot plate; however, when one or both of the crura can be seen, the direction of the pressure against the neck of the stapes is in the line of the crura. Very slight pressure laterally against the neck of the stapes may help to mobilize it (fig. 2). The amount of pressure that can be exerted on the neck of the rigid stapes without fracturing the crura is considerable.

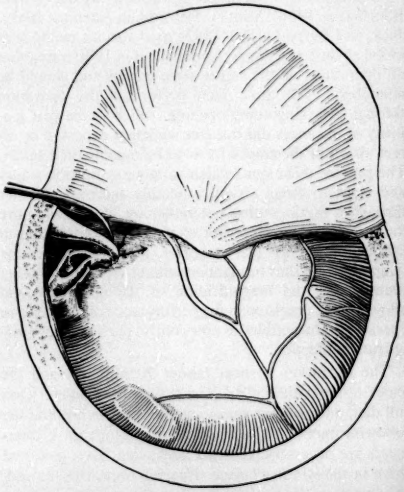

Fig. 2.—In mobilization operation, drum and skin are reflected and a wide exposure of the long process of the incus, stapes, and stapedial tendon is made after the edge of the bony canal wall is removed. Palpation is then done to determine stapedial fixation.

If during the procedure adhesions or granulations involving the ossicles or round window are encountered, they may be dealt with, using instrument no. 8 (fig. 1). A rounded and slightly bent spinal tap needle is used for suction (instrument no. 9). When the operation is fin-

ished, the drum and attached skin of the external auditory canal are replaced in their original position. The ossicular chain remains intact.

It is my conviction that generally procedures of this kind should be performed only by those skilled in endaural surgery. Before performing the mobilization operation, even the most skillful surgeon should first perform the operation on at least 50 fresh cadavers.

Results of the Mobilization Operation (Rosen) in the First 211 Consecutive Cases

In class A cases (maximum preoperative loss of 10 db. by bone conduction in the speech frequencies; average preoperative loss by air conduction in the speech frequencies, 43.9 db.), 13, or 52%, of the 25 patients in this group achieved pure tone levels of hearing between normal and 35 db., while 16, or 64%, reached these levels by speech audiometry. Twelve, or 48%, reached the 30-db. level or better by pure tones and speech audiometry. Two patients in this group achieved normal hearing. The suitability for surgery is most often determined by the high level of bone conduction, i. e., as the preoperative bone conduction recedes, the suitability for surgery diminishes.

In class B cases (a total of 92 patients) (maximum preoperative loss of 20 db. by bone conduction in the speech frequencies; average preoperative loss by air conduction in the speech frequencies, 47.5 db.), 31, or 39.3%, of 79 patients for whom pure tone and audiometry data were available achieved pure tone levels of hearing between normal and 35 db., and 38 patients, or 41.4%, of the total of 92 were found by speech audiometry to have reached these levels. Twenty-five, or 32%, of the group of 92 were at the 30-db. level or better when tested by pure tones, while 31 patients, or 34%, were found at this level by speech audiometry. In this group five patients achieved hearing within normal limits in the speech range.

In class C cases (a total of 56 patients) (maximum preoperative loss of 30 db. by bone conduction in the speech frequencies and average preoperative loss of 54.1 db. by air conduction in the speech frequencies), 49 patients were tested by pure tone and speech audiometry methods and 7 by speech audiometry alone. In 13, or 26.6%, of the 49, pure tone levels of hearing between normal and 35 db. were achieved. Sixteen patients, or 28.5%, of total class C patients were found to have reached these levels by speech audiometry. Patients in 8 cases, 16.4% of the group of 49, were found to have reached the 30-db. level or better by pure tones, while 12, or 21.4%, of the total of 56 patients reached this level by speech audiometry.

Class D cases include all patients whose preoperative bone conduction loss was greater than 30 db. at one, two, or three of the speech frequencies (500, 1,000, 2,000 cps). Of the 211 in this series, 38 patients belong in this category. In 34 of the 38 patients, the hearing loss by bone conduction preoperatively was greater than 30 db. at 2,000 cycles only, whereas at 500 and 1,000 cycles the hearing by bone conduction was better than 30 db. The preoperative pure tone air losses in the speech frequencies for D cases ranged from 43 db. to 90 db.

Ten patients in this category achieved hearing gains ranging from 15 db. to 40 db. Four in this group reached hearing levels of 35 db. or better. Of the four, one reached the 15-db. level and one the 20-db. level. Some of the patients in the D category were operated upon with the purpose of improving the hearing sufficiently to increase the benefits to be derived from a hearing aid and other rehabilitation measures. It can be seen that the mobilization operation has a much wider spectrum of applicability in all types of otosclerotic deafness than any other surgical technique.

In none of the unimproved cases did the hearing fall more than 10 db. below the preoperative level by pure tone and speech audiometry. In other words, if the hearing is not improved by mobilization, it will not be made worse. An opportunity was presented to compare the hearing in both ears in the same patient following mobilization in one ear and fenestration in the other.

A 38-year-old seaman had had bilateral progressive deafness for three or four years. In June, 1953, a left fenestration had been performed by another surgeon. The postfenestration hearing in the left ear had reached its maximum potential of 20-db. loss, since the incus is removed during the fenestration operation. In April, 1954, the right rigid stapes was mobilized, and within three weeks the right ear had gained maximum improvement (to less than 5-db. level or normal hearing), which has been maintained ever since. The maximum potential hearing improvement following mobilization is normal hearing, since the intact ossicular chain is functioning normally.

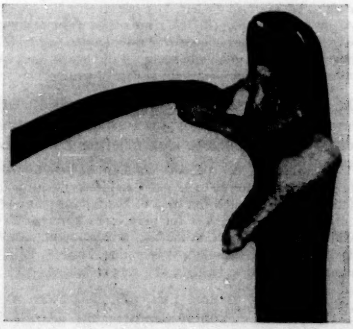

Fig. 3.—Pressure of the mobilizer (instrument no. 7) against the neck of the stapes mobilizes the foot plate without injuring the incudostapedial joint.

In the following case, mobilization was performed on a patient who had had an unsuccessful fenestration of the same ear.

A 50-year-old housewife had had a left fenestration operation performed 10 years before. Since the fenestration, the hearing in this ear had fallen to 50 db. in the speech frequencies. The operative cavity was healed. The fenestra was closed osteogenetically, since repeated mechanical irritation all around the fenestral site failed to evoke any vestibular reaction. In August, 1954, the mobilization technique was used on the unsuccessfully fenestrated ear. About 6 to 8 mm. of the lower portion of the skin flap made at the fenestration was also elevated with the drum and skin. The incus, of course, had been removed at the time of the fenestration operation. The stapes was thus exposed in its entirety. It was found rigid on palpation and was

mobilized. The hearing improved from the 50-db. level to the 30-db. level by pure tone and speech audiometry and has been maintained.

Conversely, ears unsuccessfully mobilized were fenestrated with the same results as in fenestration of ears not previously operated on, without any surgical difficulty.

Advantages Attained by Mobilization Operation

Normal Hearing.—Normal hearing is usually accepted as hearing within 10 db. of zero loss for pure tones and speech. Of patients whose preoperative bone conduction loss did not exceed 20 db., 16% achieved normal hearing following mobilization of the fixed stapedial foot plate. The ossicular chain remains intact, thus permitting the complete restoration of the normal function. No other surgical operation can restore hearing to normal. The following case illustrates normal hearing following successful mobilization.

A 24-year-old woman had bilateral progressive deafness and intermittent tinnitus for 10 years. She heard better in the subway. Her mother was hard of hearing for many years. The patient's average loss for pure tones preoperatively was 38 db. in the right ear, 42 db. in the left. Her speech reception threshold was 45 db. in both ears. The left rigid stapes was mobilized on April 1, 1954. The hearing improved on the operating table and continued to improve gradually up to a 5-db. loss, a level which has been maintained for 24 months to date of writing.

The following case illustrates that a patient with a bilateral 30-db. hearing loss due to stapedial fixation is sufficiently handicapped to seek relief for her deafness.

A 38-year-old mother of two children had had bilateral progressive deafness for 10 to 12 years and intermittent tinnitus. Her father and sister had been hard of hearing for many years. Her preoperative hearing loss for pure tones averaged 28 db. in the right ear and 30 db. in the left, with a speech reception threshold of 30 db. bilaterally. At operation, May 17, 1955, the left stapes was found to be rigid and was mobilized.

It is interesting to note that, although there was a 10-to-12-year handicapping deafness, the hearing loss was only 30 db. A patient with such a slight loss is unsuitable for fenestration. Mobilization of the fixed stapedial foot plate provided this patient with normal hearing in the ear operated on.

Almost Normal Hearing in Otosclerotic Patients with Some Evidence of Nerve Deafness in Whom Normal Hearing Is Not Possible.—Otosclerotics with a hearing loss of between 11 to 20 db. by pure tone and speech audiometry rarely experience any hearing difficulties. In the following case an almost normal level of hearing was realized through mobilization of the stapes despite significant cochlear involvement. The degree of inner ear deafness precludes the attainment of normal hearing, yet mobilization of the fixed stapedial foot plate in this case improved hearing for speech to as close to normal as was possible, 15 db.

A male, aged 53, had had bilateral progressive deafness for 10 years. He wore a hearing aid constantly for six years. His average loss for pure tones was 52 db. in the right ear and 50 db. in the left ear. His speech reception threshold was 50 db. in both ears. On Jan. 11, 1954, the very rigid left stapes was mobilized. The hearing improved to the 15-db. level by pure tone and speech audiometry and has remained at that level ever since.

Useful Binaural Hearing.—Patients with moderate to severe unilateral deafness, in which the hearing in the other ear is normal or shows only a slight loss, often complain of difficulty in hearing speech in a noisy environment. Otosclerotics who wear hearing aids have the same difficulty, since they, too, are hearing unilaterally through the hearing aid. This difficulty can be overcome only by binaural reception such as that provided by the two ears hearing about equally. While it is well known that otosclerotics often hear better in noisy places, this occurs only when the hearing loss is relatively equal in both ears. With the aim of achieving binaural hearing, it was decided in the case below to mobilize the right stapes in the hope that the hearing in this ear would reach or surpass that of the better left ear, which had been successfully fenestrated, and thus result in binaural, unaided hearing.

A woman, aged 43, had had bilateral progressive deafness for 25 years. A successful left fenestration was performed by another surgeon in 1945. Nine years later (1954) she decided to have the mobilization operation on the right ear. The speech reception threshold of the left (fenestrated) ear was 30 db., with an average pure tone loss of 30 db. The right ear showed an average pure tone loss of 50 db. and a speech reception threshold of 55 db. Successful mobilization of the right stapes on Dec. 3, 1954, resulted in hearing in the right ear of 25 db., which was slightly better than the hearing in the successfully fenestrated left ear. Binaural hearing was thus achieved.

Removal of the Conductive Component (Stapedial) in Mixed Deafness (Cochlear and Stapedial).—The following case best illustrates a severe mixed deafness in which the hearing loss due to stapedial fixation was completely eliminated by mobilization, leaving the cochlear deafness. The improved hearing following elimination of that portion of the deafness due to stapedial fixation allowed more effective use of the hearing aid.

A 28-year-old man had had bilateral progressive deafness for over 10 years. An unsuccessful right fenestration performed in Bucharest in 1945 was followed by facial palsy, from which he recovered in six months. There was severe tinnitus in both ears. On Aug. 10, 1952, the left stapes was mobilized. Hearing dramatically improved on the operating table. The hearing by air conduction in the left, unfenestrated ear preoperatively showed an average pure tone loss of 82 db. Hearing by bone conduction, though poor, indicated the possibility of improving his hearing to the degree that the conductive element of his deafness might be corrected. The hearing by air conduction postoperatively showed an average loss of 47 db. for 500 through 2,000 cps, with hearing at 20 to 25 db. at 125 and 250 cps respectively. The improvement is significant in terms of the value to be derived from the use of a hearing aid.

Successful Use of Hearing Aid in Extreme Deafness.—The gain or amplification of the strongest commercial hearing aid is insufficient to provide comfortable hearing for ordinary conversation in a patient with a hearing loss in the better ear that is greater than 85 db. Any significant improvement in hearing in such profound deafness increases greatly the benefits to be derived from the use of a hearing aid.

A 45-year-old woman had had bilateral rapidly progressive deafness since the age of 18. The speech reception threshold was 100 db. in the left ear and 95 db. in the right. The speech discrimination test had to be performed at only 10 and 15 db. above the speech reception threshold of the right and left ears respectively. At these low sensation levels, her discrimination scores were relatively high (58% and 62%), which suggested

the feasibility of mobilization. The patient complained of her inability to hear adequately with maximum amplification of her hearing aid. On Nov. 10, 1954, her very rigid stapes was mobilized. The pure tone average in the ear operated on rose from 83-db. loss to 68-db. loss, and the speech reception threshold rose from 95 db. to 75 db. The discrimination score in the ear operated on rose from 62% to 94% at the same testing level used preoperatively, 110 db. above zero hearing loss for speech. Since mobilization, the patient reports greatly improved hearing with the hearing aid.

Summary

The ultimate goal of any treatment for otosclerotic deafness is the restoration of normal hearing in both ears. Mobilization of the fixed stapes is capable of achieving this goal where there is as yet no cochlear (perceptive) involvement. The goals of mobilization vary with each patient's hearing potential. Through successful mobilization it is possible to realize the full hearing potential in the various degrees of otosclerotic deafness.

Mobilization can be successful in the same types of cases in which fenestration can succeed. Mobilization can be successful in cases with a handicapping hearing loss of 30 db. or less, a loss not yet great enough to be suitable for fenestration. In moderate and profound otosclerotic deafness, the mobilization operation can restore useful aided or unaided hearing. In cases of extreme deafness, successful mobilization must be followed up by the selection of a hearing aid and auditory training to realize the full benefits to be gained from the operation.

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CONTROL OF CHRONIC PAIN BY DL-ALPHA ACETYLMETHADOL

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• *The analgesic effect of racemic alpha acetylmethadol was studied in 49 patients suffering chronic pain due to cancer, 10 recovering after surgery, and 17 in chronic or transient pain from other causes. Doses of 5 to 10 mg. given three or four times daily were highly effective on continued use.*

Good relief from pain was obtained by either oral administration or subcutaneous injection. A few patients complained of lethargy. Hypnotics were usually needed for sleep. It was possible in several patients to discontinue use of frequent injections of large doses of morphine or meperidine and to change over completely to the oral use of acetylmethadol without causing withdrawal symptoms.

Constipation was bothersome with large daily doses (30 to 50 mg.). Other side-effects were infrequent. The toxic effects of cumulation with large doses can be avoided by taking into account the patient's metabolic and excretory status. In the majority of patients in this series, the oral administration of acetylmethadol has afforded relief from chronic pain for several months without severe untoward effects.

One of the most vexing therapeutic problems is to keep the patient with chronic pain reasonably comfortable without resorting to opiates. Much can be done to relieve the pain of cancer or other chronic conditions either before using narcotic analgesics or later to supplement and prolong their beneficial effects. Often worth trying are procedures such as chordotomy, sympathectomy, endocrine gland removal, nerve block, intravenous administration of procaine, selective radiation, and administration of nitrogen mustards, radioactive chemicals, or hormones. Unfortunately, not all patients can avail themselves of these measures and many refuse surgery. At best, the pain alleviation provided by these various procedures is short-lived. Sooner or later, recourse must be had to the opiate analgesics.

When the decision is made to employ narcotics, the physician usually first tries preparations or combinations of the milder opiates, such as codeine administered orally. It is often possible to continue oral administration for long periods of time with codeine alone or by alternating it with some of the stronger analgesics along with the judicious employment of the barbiturates, the antihistaminics, and the newer so-called potentiating agents. In many cases, however, administration by hypodermic of opiates is started early in the management of chronic pain with little thought being given to the consequences. Not only is injection by hypodermic inconvenient, costly, and dangerous, but, with the narcotic analgesics, it leads quickly to tolerance and addiction.

An ideal analgesic suitable for the management of chronic pain would be one that is well tolerated and effective orally, is potent and able to provide prolonged pain relief, causes but few annoying untoward actions, and is slow to develop tolerance and addiction. The purpose of this paper is to report the clinical trial of a new synthetic analgesic *dl*-alpha acetylmethadol hydrochloride (6-di-

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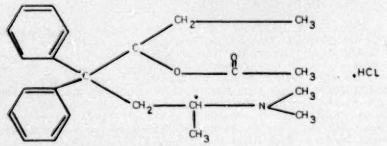
Drs. Augustus Gibson and Elmer Alpert, of Medical Division, Merck & Co., Inc., Rahway, N. J., furnished the synthetic narcotics used in this study. Chlorpromazine was supplied through Dr. Edwin Fellows and Mr. William Kirsch, Smith, Kline & French Laboratories, Philadelphia.

methylamino-4,4-diphenyl-3-heptanylacetate hydrochloride), which, we feel, meets many of these requirements. Acetylmethadol has been found to be of particular benefit in providing relief from pain to the patient with advanced metastatic cancer. We have been able to continue oral administration of this new compound for long periods of time with considerable success and believe our methods and results merit reporting at this time.



Structural formula of alpha acetylmethadol hydrochloride (status at position * governs sterioisomerism; from Merck mimeographed letter [2]).

Chemistry and Pharmacology

Acetylmethadol (see figure) is a synthetic analgesic made from the two isomers of methadone.[1] The racemic (*dl*) preparation is an equimixture of each acetylmethadol isomer. Early laboratory studies with the separate isomers in comparison with *dl*-methadone showed the levo isomer to have a delayed onset of action and toxicity and to be only one-fourth as analgesic as *dl*-methadone. The dextro isomer, however, acted as rapidly, did not show delayed toxicity, and was twice as active as racemic methadone. The racemic acetylmethadol appeared similar to methadone in onset of action, duration, and potency.[2] We [3] found *dl*-alpha acetylmethadol to be more constipating than morphine in rats and rabbits when given in equivalent analgesic doses, but tolerance is less likely to develop.

Used clinically, the levo acetylmethadol was found on repeated subcutaneous administration to cause delayed toxic effects.[4] With the racemic mixture, Fraser and Isbell [4a] observed that single injections of 30 mg. in man produced intense effects in 30 minutes that lasted 30 hours. No reports other than our preliminary abstracts [5] have appeared as yet on the clinical use of orally administered *dl*-alpha acetylmethadol.

Patients and Materials

Patients.—Most of our patients were started on acetylmethadol therapy in the hospital (in most cases at the Multnomah County Hospital, also at Providence and Physicians and Surgeons hospitals). Many continued treatment when discharged and were followed at home or in a nursing home. Other ambulatory patients were seen in the clinic, and several were referred by other physicians. All patients were closely observed for the first few weeks and were seen at frequent intervals thereafter.

Causes of Pain.—In order to tabulate data and results, the 76 patients reported here have been placed in one of three groups, depending on the length of time treated. Table 1 lists the causes of pain, the number of men and of women, and the average age for each group. Sixteen hospitalized patients had postoperative or transient pain and another 11 chronic pain due to causes other than cancer. Forty-six had chronic pain from metastatic cancer, two from plasma cell myeloma, and one from sarcoma of the shoulder.

Dosage and Administration.—Acetylmethadol was available in 5-mg. tablets or ampuls. Oral or subcutaneous administration was begun cautiously using small doses. The use of other narcotics was either stopped or continued in reduced dosage and frequency with at least an interval of two hours before or after administration of acetylmethadol. At first, dosages of 5 or 10 mg. were given two or three times a day. If large doses of other narcotics had been used previously, 10 mg. of acetylmethadol was used three or four times per day. Adjustments in dosage were made as necessary by giving amounts such as 10 mg. three times a day, 10 mg. for the first and last daily dose with one to three interspaced 5-mg. doses, or three to four 5-mg. doses. As pain severity increased and as the patient's condition deteriorated, increases in dosage to 10 mg. four or five times a day were allowed. Repeated doses of 15 mg. were used in only two patients with terminal conditions.

Supplementary Analgesics and Adjuncts.—Since all but one patient had received narcotic analgesics before using acetylmethadol, many were already partly addicted and tolerant to these agents. Table 2 shows the number of patients considered as addicted, those who were continued for limited periods on reduced dosages of previously administered narcotics, and the number allowed to use supplementary analgesics such as codeine by mouth in order to provide rapidly acting but short-lasting pain relief between the evenly spaced doses of acetylmethadol.

Antiemetics such as diphenhydramine (Benadryl) hydrochloride, dimenhydrinate (Dramamine), and, later, chlorpromazine (Thorazine) hydrochloride were used to allay nausea or emesis. Hypnotics were usually necessary for sleep even when total daily amounts of from 40 to 50 mg. of acetylmethadol were being given.

TABLE 1.—*Causes of Pain in Seventy-Six Patients Receiving Acetylmethadol*

	Period Treated			
	2-10 Days	10-30 Days	Over 30 Days	Total
No. of patients	26	19	31	76
Women	14	8	17	39
Men	12	11	14	37
Age (av.), yr.	47	59	58	..
Cause of pain:				
Cancer, breast	1	1	7	9
Cancer, lung	2	6	4	12
Cancer, other types of	7	8	13	28
Postoperative state	10	..	..	10
Miscellaneous	6	4	7	17
No. requiring large doses of analgesics (addicted?)	7	10	19	36

Methods of Treatment

Administration by Hypodermic.—Subcutaneous injections were used in 12 of the first 34 patients and one of the last 42 patients treated. Table 3 shows that eight patients were given acetylmethadol both hypodermically and orally, while five received only the injectable form. Injections were given when trial was started in some patients, since they had been receiving other analgesics

by this route. Three of the patients who claimed that they could not swallow tablets or that the tablets caused nausea were given injections of the drug and made no further complaint. Only the one patient among those last treated continued to vomit occasionally when the means of administration was changed from oral to parenteral. She was dying of widespread metastases from cancer of the breast, and her emesis showed no causal relationship to drug injection. Of the 13 patients who received injections, 3 were given the injectable form exclusively for periods of 35, 20, and 19 days. Another four, also given tablets either before or afterward, received only injections of the drug for periods of 21, 15, 14, and 9 days. None of these patients showed any evidence of undue cumulative effect or other untoward action from administration of acetylmethadol by hypodermic. Similarly, no especial differences in the degree or duration of relief of pain, compared to results of oral administration, were observed.

tion of the 25-mg. tablet three or four times a day and one or two hours before or after use of acetylmethadol. No untoward effects were noted, and it was felt that chlorpromazine proved much more effective than other antiemetics in controlling nausea and vomiting in the cancerous patient with metastases. Potentiation by chlorpromazine of the analgesic effects of acetylmethadol was not especially noticeable in these cases.

Hydergine (methanesulfonates of dihydrogenated ergotoxine alkaloids) was given to four patients for periods of a week or longer to observe whether or not small divided doses could provide analgesic potentiation.[6] However, no conclusions could be drawn in this instance.

Course of Treatment

Group 1.—Twenty-two of the 26 patients in group 1 (those treated from 2 to 10 days) were among those first given acetylmethadol. Most of these patients suffered postoperative or transient pain and consequently were given only small doses of the analgesic for a short period. Three received the drug by injection, while 23 used only the tablets (table 3). A longer trial of acetylmethadol was interrupted by the transfer of one patient with persistent

TABLE 2.—*Use of Analgesics and Adjuncts Before or During Trial of Acetylmethadol*

Analgesic or Adjunct *	Route Given	Period Treated: 2-10 Days, Before Trial	2-10 Days, During Trial	10-30 Days, Before Trial	10-30 Days, During Trial	Over 30 Days, Before Trial	Over 30 Days, During Trial
No. of patients		26		19		31	
No. addicted (?)		7		10		19	
Codeine compound	Oral	13	..	10	2	14	7
Codeine	Oral	..	..	2	1	2	1
	Parenteral	1	1	1	1	2	..
Meperidine hydrochloride	Oral	4	..	1	..	1	1
	Parenteral	6	..	6	1	9	1
Morphine	Oral	1	..	..	..	..	..
	Parenteral	8	1	3	1	8	2
Dihydromorphinone hydrochloride	Parenteral	2	..	..	..	1	..
Levorphanol tartrate	Oral	..	..	..	..	1	1
	Parenteral	..	..	..	..	..	1
dl-Dromoran	Parenteral	..	..	..	..	..	1
l-isomethadone	Oral	..	..	..	..	1	..
	Parenteral	..	1	..	..	..	..
Pantopon (alkaloids of opium)	Rectal	..	..	1	1	..	..
6-methyl-Δ^8-desoxymorphine hydrochloride †	Oral	..	..	..	..	..	2
	Parenteral	..	..	..	..	..	1
Diphenhydramine hydrochloride	Oral	..	..	..	1	..	3
Dimenhydrinate	Oral	..	1	..	..	..	..
Chlorpromazine	Parenteral and oral	..	..	..	2	..	7
None	.....	..	23	..	10	..	6

* Barbiturates or other hypnotics not included.
† MK-57, a new synthetic analgesic under pharmacological and clinical investigation.

Oral Administration.—Many of the patients seen early in the trial were given acetylmethadol in tablet form. Although the majority were treated for short periods (table 3), several continued to receive the drug orally for over a month or longer periods. Including the last 41 patients, a total of 63 patients was treated exclusively with the orally given form.

Use of Other Drugs.—A few patients were allowed for limited periods to continue receiving reduced doses of the previously administered narcotics or to continue their use indefinitely as supplementary analgesics. On the other hand, it was possible in several patients to discontinue use of frequent injections of large doses of morphine or meperidine and to administer orally only acetylmethadol. No withdrawal symptoms caused by the previous use of opiates were seen when acetylmethadol therapy was substituted.

Administration of Other Drugs.—Nine patients were given chlorpromazine over extended periods of time. This drug was usually given intramuscularly for the first three or four doses and then continued with administra-

TABLE 3.—*Data and Results of Trial of Seventy-Six Patients*

	Period Treated: 2-10 Days	10-30 Days	Over 30 Days	Total
No. of patients	26	19	31	76
Average no. of days treated	5	18	117	..
Total drug given, gm.	2	8	80	90
Routes administered:				
Parenteral only	2	2	1	5
Parenteral or oral	1	3	4	8
Oral only	23	14	26	63
Status at conclusion of trial:				
Died during trial	4	10	19	33
On other or no therapy	22	9	8	39
Still on acetylmethadol therapy	..	..	4	4
Other analgesics used in patients with terminal conditions:				
Morphine	..	4	6	10
Meperidine	..	1	2	3
Dihydromorphinone	..	1	..	1

nausea to *l*-isomethadone therapy and by death in three patients with terminal conditions. On termination of trial, 15 patients were again given the previously used analgesic, 2 were placed on *l*-isomethadone therapy, and 5 were sent home with no further analgesic medication. During trial, only three required supplementary analgesics: one, an addict, received a few injections of morphine; one with cancer of the tongue and throat with difficulty in swallowing was given several injections of *l*-isomethadone; and the third, an elderly man dying of lung cancer, received codeine hypodermically several times (table 2).

Groups 2 and 3.—The two other groups, comprising 50 patients, may be considered together since all suffered chronic pain. In 29 the use of previously prescribed narcotics was considered sufficient to have developed some degree of tolerance and addiction. Because of addiction and since most of them suffered severe pain, transfer to acetylmethadol therapy was made, usually by starting with doses of 10 mg. given from two to four times a day. Continuation of previously administered narcotics was permitted in six patients who were allowed occasional doses of codeine-acetylsalicylic acid compound, in one given codeine hypodermically, in another given several injections of morphine the first three days, and in two who were given levorphanol (Levo Dromoran) tartrate. Later during this study supplementary doses of short-acting analgesics were permitted some patients receiving daily doses of from 40 to 50 mg. of acetylmethadol and whose conditions were becoming progressively worse (table 2).

TABLE 4.—*Relief of Pain and Untoward Effects Noted in Seventy-Six Patients Treated with Acetylmethadol*

	Period Treated			
	2-10 Days	10-30 Days	Over 30 Days	Total
No. of patients	26	19	31	76
Degree of relief:				
Excellent	3	3	8	14
Satisfactory	18	14	12	44
Fair	4	2	10	16
Poor	..	..	1	1
Uncertain	1	..	..	1
Untoward effects:				
Constipation	..	..	10	10
Nausea	2	1	5	8
Vomiting	4	4	9	17
Lethargy	3	3	7	13
Cumulation	3	3	3	9
Dizziness	2	1	3	6
Confusion	..	4	1	5
Hallucinations	..	2	1	3
Severe depression	2	..	..	2
None	13	2	7	22

Results

Length of Trial.—The period of time during which acetylmethadol was administered is indicated in table 3 by the range of days over which each group of patients was treated. While nine of the first patients treated postoperatively were purposely given the drug for only 2 or 3 days, six other cancer patients given acetylmethadol at this time were continued on the therapy for longer than 30 days. Eleven patients have been treated for over four months and seven over six months, two of whom are still living and taking acetylmethadol. Another patient had taken acetylmethadol continuously for 392 days before administration was discontinued. Thirty-three continued taking acetylmethadol until death. Of the 43 living when further trial or study was terminated, 25 were either returned to a regimen of the previously used analgesic or medication was stopped; 14 patients with terminal conditions were transferred to use of injections of morphine, meperidine, or dihydromorphinone, and four, including the two mentioned above, are still using acetylmethadol.

Relief of Pain.—Appreciable relief of pain following injection of acetylmethadol occurred within 20 to 30 minutes. Following oral administration, relief was noted usually within 40 minutes, although several patients reported noticeable effect within 20 to 30 minutes. The average duration of analgesic effect was between four and five hours.

We attempted to estimate the degree of relief of pain provided by acetylmethadol by comparison with that obtained with other narcotics given before or after acetylmethadol, by frequent questioning and observation of the patient, and by noting the results of occasional adjustments in dosage, which was increased or decreased to keep the patient relatively pain-free without undue side-effects.

Table 4 shows that, for the small doses of acetylmethadol used in the first group, relief of pain was considered in 3 patients to be as excellent as, and better than, that obtained from other analgesics; in 18, as satisfactory and as good as that previously experienced; in 4, fair or less satisfactory than before or afterward; and, of uncertain evaluation in one patient who died on the second day of trial.

In the other two groups (50 patients), adequate relief was provided over long periods of time in practically all instances. The degree of relief was considered in 11 patients to be excellent; in 26, satisfactory; in 12, fair, since most of these patients also used supplementary analgesics; and in one, poor, since the patient continued receiving large, frequent doses of morphine. Acetylmethadol was used exclusively for relief of pain in 23 of the 26 patients treated from 2 to 10 days, in 10 of the 19 treated for up to 30 days, and in 6 of the 31 who received acetylmethadol for prolonged periods of time.

Untoward Effects.—With small doses of acetylmethadol, untoward effects were minimal. None were observed in 13 of the 26 patients treated for less than 10 days or in 9 in the other two groups (table 4). Six in the first group complained of nausea or vomiting caused by the tablets; this complaint was not bothersome enough to stop treatment except in one patient. In the other two groups, 19 patients were nauseated or vomited at some time during trial of acetylmethadol. However, since many had brain metastases or cancerous involvement of the gastrointestinal tract, it was difficult to determine to what degree acetylmethadol was responsible for these symptoms.

Moderately severe constipation was complained of by 10 of the 31 patients treated for longer than 30 days; in spite of the routine use of laxatives and enemas, this was

especially noticeable when larger doses were being used in the bedfast, anoretic patient. In three bedfast patients it was necessary to remove fecal impactions several times.

Tolerance and addiction to acetylmethadol seemed slow to develop, as indicated by the fact that after starting therapy most patients were able to continue at the same dosage level for long periods of time. In several cases it was possible to withdraw use of acetylmethadol by gradual reduction in dosage.

Early cumulative effects evidenced by slight depression or the ability to skip one or more doses of acetylmethadol because of freedom from pain were noted in those patients taking more than 20 mg. per day and who had not developed tolerance to other narcotics. A total of 6 patients complained of transient periods of dizziness, while 13 said they felt "dopey" or lethargic at times or when doses were in excess of their analgesic requirements. Severe depression attributable to intolerance to acetylmethadol occurred in two patients with terminal conditions of cancer who for several days were given oral doses of acetylmethadol averaging only from 20 to 30 mg. per day.

Comment

The outstanding advantage of therapy with acetylmethadol in the management of continued chronic pain is that often the same dosage may be used over several months to keep the patient comfortable without severe side-effects. While tolerance to acetylmethadol occurs, it appears slowly and only when larger daily doses of about 30 or 40 mg. are employed. Addiction to acetylmethadol is mild, judging from our observation of a few patients who had been maintained on acetylmethadol therapy for long periods of time and whose therapy was changed to the use of the usual doses of other narcotics without their showing withdrawal symptoms. In some patients who had depended on the use of acetylmethadol for a long time the oral administration of short-acting, less potent analgesics such as codeine or 6-methyl-Δ^6-desoxymorphine hydrochloride (MK-57) two or three times a day between doses of acetylmethadol effectively supplemented analgesia. This seemed preferable to increasing the dose of acetylmethadol.

It is extremely difficult in patients with metastatic cancer involving the brain and/or the gastrointestinal tract to determine whether anorexia, nausea, vomiting, constipation, and insomnia are drug-induced or simply associated with the disease. Nausea or vomiting was a minor complaint, occurred infrequently, and, if associated with the disease, was easily controlled by antihistaminics or chlorpromazine. Constipation was not easily combated by the use of laxatives; the danger of fecal impaction, especially in the bedfast patient taking large doses of acetylmethadol, is a real one. Severe depression from use of acetylmethadol may occur, especially in the aged patient who has not developed much tolerance to narcotics and if the use of larger doses is continued.

Summary and Conclusions

The racemic form of alpha acetylmethadol hydrochloride was administered subcutaneously and orally for the relief of postoperative and chronic pain in 76 patients. While 13 patients showed satisfactory pain relief when given acetylmethadol by injection, the preparation was used only orally in the other 63. Forty-nine patients had chronic pain due to cancer, 10 patients were in postoperative states, and 17 had transient or chronic pain from various causes. All but one patient had received narcotic analgesics prior to trial of acetylmethadol, and 36 were considered as partly addicted. Usually, change to therapy with acetylmethadol was easily accomplished with initial doses based on the patient's condition, severity of pain, and prior analgesic requirement. Doses of from 5 to 10 mg. given three or four times daily were well tolerated, safe, and highly effective on continued use. Good relief of pain with a minimum of untoward effects was provided both the ambulatory or the bedfast patient in the hospital or being cared for at home or in nursing homes. Transient nausea or vomiting occurred infrequently; when due to extensive metastases these symptoms were controlled by antihistaminics or chlorpromazine. With large daily doses (30 to 50 mg.) of acetylmethadol, constipation was bothersome. A few patients complained of lethargy, usually during early use of the drug and when using larger doses than necessary. Relatively long duration (four to five hours) of analgesic effect was obtained from single oral doses of acetylmethadol during the first two or three months of its trial. However, the eventual development of tolerance and, more likely, the progressive deterioration of the patient shorten this prolonged action and necessitate an increase in dosage. We believe that slow cumulation of the drug explains the continued analgesic effectiveness and prolonged action of acetylmethadol when given orally; however, cumulation leading to severe toxic effects may occur if too large doses are used or account is not taken of the patient's metabolic and excretory status.

Since the majority of our patients with chronic pain due to cancer or other causes have depended upon oral administration of acetylmethadol for satisfactory relief of pain without severe untoward effects for periods of over several months, we feel that this new analgesic is safe and compares favorably to other narcotics now used in the management of chronic pain. Its further clinical trial for the relief of the pain of cancer is warranted.

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HYDROXYZINE (ATARAX) HYDROCHLORIDE IN DERMATOLOGICAL THERAPY

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• *Certain dermatoses that are generally recognized as affected by psychogenic stimuli were treated with hydroxyzine hydrochloride, a tranquilizing drug administered by mouth. The initial dosage was 10 mg. four times a day in 48 patients and 25 mg. four times a day in 111 patients. The ataraxic (relaxing) effect, as judged from the statements by the patients, was satisfactory in 132 and fair or insignificant in 27. The condition of the skin was evaluated objectively in 41 patients who had general atopic dermatitis, localized neurodermatitis, pruritus ani, or factitious dermatitis and who were given the drug and a placebo alternately. Of the 41, 36 showed clinical improvement while taking the drug and recrudescence while taking the placebo.*

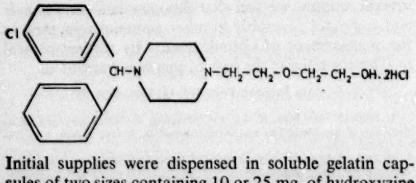
Side-effects, which included headache, sleepiness, dryness of the mouth, and itching, were generally infrequent and mild. In one case the headache made it necessary to discontinue giving the drug. No evidence of damage to the blood, kidneys, or liver was seen in patients who took the drug for six weeks or more. The demonstrated tension-relieving action of the drug explained the objective evidence of its usefulness in dermatology.

The literature contains many references to the effect of psychogenic stimuli in the production of such dermatoses as urticaria, lichen planus, neurodermatitis, seborrheic dermatitis, psoriasis, pruritus ani, pruritus vulvae, and other eruptions.[1] The barbiturates, bromides, and other sedatives and sedative-stimulant mixtures have proved to be useful as adjunctive therapy, but prolonged administration of these compounds may lead to central depression, skin eruptions, habit formation, and other undesirable side-effects.[2] The recent development of a group of drugs whose primary therapeutic effect is ataraxia (relief from tension) has added less reactive and more effective compounds for use by the practitioner.[3]

Hydroxyzine (Atarax) hydrochloride is a new tranquilizing drug that is currently under clinical investigation. Evaluating the effect of any drug on emotional stimuli is extremely difficult, because the results must be based primarily on subjective statements. The only objective method by which these drugs may be evaluated, in our experience, is by administration of alternate courses of ataraxic drugs and placebos and by observation of clinical changes in the skin. The following report presents a subjective and objective evaluation of the atarax value of this drug in dermatological therapy.

Materials and Methods

The Drug.—Hydroxyzine hydrochloride, 1-*p*-chlorobenzhydryl-4-[2-(2-hydroxyethoxy)-ethyl]-diethylenediamine dihydrochloride, is a water soluble white crystalline solid. The structural formula is given below.



Initial supplies were dispensed in soluble gelatin capsules of two sizes containing 10 or 25 mg. of hydroxyzine hydrochloride. The placebo was contained in identical capsules. There was no identifying label, so that it was impossible to distinguish between the active drug and the placebo by appearance. The drug is now supplied in enteric-coated tablets, the 10 mg. tablets being orange colored and the 25 mg. tablets green. The placebo tablets are similar in size and color.

Patient Selection.—All patients were adults ranging in age from 17 to 72 years. The studies were conducted in the outpatient department of the University Hospital and in our private practices. There were 67 white males, 2 Negro males, 88 white females, and 2 Negro females. All patients had some eruption in which emotional tension was considered to be a factor.

Administration of Drug.—Initial dosage of hydroxyzine hydrochloride in 48 patients was 10 mg. after each meal and at bedtime and, in 111 patients, 25 mg. after each meal and at bedtime. It was decided to administer the drug after meals because the first four patients treated with hydroxyzine hydrochloride took the drug before meals and complained of gastric distress and some nausea. This did not occur if food preceded the drug administration. In seven patients it was necessary to increase the dose from the 10 mg. schedule to the 25 mg. schedule, and in eight it was possible to reduce the 25 mg. schedule to the 10 mg. schedule.

To facilitate objective evaluation, substitution therapy with placebo medication was used. This portion of the study was conducted on patients who had generalized atopic dermatitis, localized neurodermatitis, pruritus ani, and factitious dermatitis. Results were based on the increase or decrease in excoriations or erythema observed by the investigators. During this type of evaluation, no change was made in local therapy. Subjective improvement was noted and reported by the patient. To determine the ataraxic value of hydroxyzine hydrochloride, a comparison study with other tranquilizers was made on 64 patients. This group of patients received alternating courses of a sedative drug, or other tranquilizers, and hydroxyzine hydrochloride.

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This study was supported by a grant-in-aid from J. B. Roerig & Company, Chicago.

Laboratory Studies.—Urinalyses and hemograms were performed on 71 patients who had been under treatment with hydroxyzine hydrochloride for a minimum of six weeks. Sulfobromophthalein (Bromsulphalein) tests were made on 21 patients who had received hydroxyzine hydrochloride for at least eight weeks.

Results

The results of this study are divided into three parts: (1) subjective evaluation, (2) objective evaluation, and (3) comparative evaluation.

Subjective Evaluation. — Hydroxyzine hydrochloride was administered to 159 patients with various dermatoses (see table). Ataraxic effect was satisfactory in 132 patients, who stated that they experienced some degree of release from previously existing tension. The calming effect was most pronounced in patients with atopic dermatitis, neurodermatitis, factitious dermatitis, lichen planus, pruritus ani or pruritus vulvae, and urticaria. Statements made by 15 patients indicated that in these persons the tranquilizing effect was only fair, and in 12 patients hydroxyzine hydrochloride therapy was ineffectual.

Seven patients reported drowsiness, which disappeared after two or three days of continued medication. Two patients noted persistent sleepiness. Four patients who had received the medicament for one week complained of dryness of the oropharynx, but this symptom was not severe and it was not necessary to discontinue administration of the drug. The first four patients complained of "a fluttering feeling in the stomach," but, when the medicament was taken after meals, the symptoms subsided. Slight itching was noted by one patient who had been taking hydroxyzine hydrochloride for two weeks, and it became necessary to discontinue administration of the drug and substitute another compound. One patient developed severe headache after taking hydroxyzine hydrochloride for one week, but, when administration of this drug was discontinued and phenobarbital (15 mg. four times a day) substituted, the headaches disappeared. On administration of placebo tablets, the patient did not develop headaches, but, when hydroxyzine hydrochloride was readministered, the headaches recurred.

Objective Evaluation. — Forty-one patients were treated with alternating courses of hydroxyzine hydrochloride and a placebo. The objective evaluation was based on the clinical increase or decrease in erythema, excoriations, and the extent of lesions. This portion of the study was limited to observation of patients with atopic dermatitis, localized neurodermatitis, eczematized pruritus ani or pruritus vulvae, and factitious dermatitis, because of the ease of evaluating the objective phenomena. Of the 12 patients with atopic dermatitis, in 11 the condition was noticeably improved while they were receiving hydroxyzine hydrochloride. Of the 10 patients with localized neurodermatitis, the condition of 9 improved while they were receiving active medication with hydroxyzine hydrochloride. Of the 12 patients with eczematized pruritus ani or pruritus vulvae, 11 were definitely benefited by the administration of hydroxyzine hydrochloride. This drug was of value in the treatment of five of the seven patients with factitious dermatitis. The 36 patients in whom clinical improvement was noted while they were receiving the drug developed more excoriations, more extensive lesions, or an increase in erythema when the placebo was substituted.

Comparative Studies with Other Tranquilizers or Sedatives.—Evaluation was based on subjective evidence obtained from the statements of patients treated with alternate courses of hydroxyzine hydrochloride and other tranquilizers. Of the 33 patients treated with phenobarbital (15 mg. four times daily), 2 stated that the ataraxic effect was good, while 31 noted only a slight effect. When hydroxyzine hydrochloride was substituted, these 31 patients stated that the ataraxic effect was superior to that of phenobarbital. Of two patients who received butabarbital (Butisol) sodium (15 mg. four times daily), one preferred this drug and the other preferred hydroxyzine hydrochloride. Thirteen patients received alternating courses of chlorpromazine (Thorazine) hydrochloride (25 mg. four times daily) and hydroxyzine hydrochloride, and, of these, two stated that hydroxyzine hydrochloride was superior to chlorpromazine, two stated that chlorpromazine produced a more satisfactory effect, and nine patients noted no difference. Nine patients were treated with alternating courses of meprobamate (Miltown) (400 mg. four times daily) and hydroxyzine hydrochloride, and no difference between the two drugs was noted by any of them. One patient preferred hydroxyzine hydrochloride to bromisovalum (Bromural) (300 mg. four times daily). Four patients who had previously received treatment with antihistaminic drugs in variable doses stated that hydroxyzine hydrochloride had a superior ataraxic effect.

Evaluation of Hydroxyzine Hydrochloride Based on Statements Made by 159 Patients *

Condition	No. of Patients	Ataraxic Effect			Adverse Reactions	
		Good	Fair	Poor	Mild	Severe
Atopic dermatitis (extensive)	36	31	4	1	4	..
Neurodermatitis (localized)	33	30	..	3	2	1
Factitious dermatitis	7	6	..	1	1	..
Psoriasis	17	11	4	2	2	..
Dermatitis herpetiformis	4	2	2	..	..	..
Lichen planus	5	5	..	..	1	..
Nummular eczema	2	2	..	..	1	..
Dyshidrosis	15	11	2	2	2	..
Alopecia areata	4	3	1	..	..	..
Pruritus ani or pruritus vulvae	12	12	..	..	..	..
Urticaria	5	5	..	..	2	..
Seborrheic dermatitis	17	12	2	3	..	..
Rosacea	2	2	..	..	..	..

* These patients received 10 to 25 mg. of hydroxyzine hydrochloride four times daily.

Laboratory Studies

Urinalyses and hemograms of 71 patients who had received hydroxyzine hydrochloride for a minimum of six weeks showed no abnormality. No abnormality was noted in the sulfobromophthalein test in 21 patients who had received hydroxyzine hydrochloride for a minimum of eight weeks.

Comment

Hydroxyzine hydrochloride is a drug that produces a state of relaxation and relief from tension. It is valuable complementary therapy for conditions characterized by cutaneous eruptions in which emotional tension is a factor. This study indicates that it is as effective as other tranquilizers presently available. Long-term administration of hydroxyzine hydrochloride did not cause abnormalities in the hemopoietic system, in the urinary tract, or in liver function in the patients studied. Adverse effects have been minimal. Observations recorded in this study indicate that treatment should be initiated with a dosage schedule of 10 mg. of hydroxyzine hydrochloride after each meal and at bedtime, and, if this does not produce the desired effect, the dose may be increased to 25 mg., four times daily.

Summary and Conclusions

Hydroxyzine (Atarax) hydrochloride, an atarax drug, was used in treatment of 159 patients with various dermatoses in which emotional stress was thought to be a factor. Subjective evaluation led to the conclusion that its effect was satisfactory in 132 patients, who stated that they experienced some degree of relief from previously existing tension. It was necessary to discontinue administration of the drug in one patient because of severe headache. Other mild reactions such as continued sleepiness, dryness of the mouth, and slight itching were infrequent.

Objective evaluation in 41 selected patients led to the conclusion that hydroxyzine hydrochloride is valuable adjunctive therapy in the treatment of patients with dermatoses in which emotional tension is a factor. Comparative studies based on subjective evidence led to the conclusion that hydroxyzine hydrochloride produced as satisfactory an ataraxic effect as other tranquilizers presently available.

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INTRAVENOUSLY GIVEN UROGRAPHIC MEDIUMS

COMPARATIVE STUDY OF EIGHT HUNDRED CASES

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and
Maxwell H. Poppel, M.D., New York

• *The relative advantages of four intravenously given urographic mediums were studied by using each in a group of 200 patients. The lowest incidence of unpleasant reactions was obtained with a substance that is a mixture of the sodium and methylglucamine salts of diatrizoate.*

The purpose of this paper is to evaluate and compare the four drugs now commonly used as intravenously given urographic mediums. Eight hundred patients were divided into groups of 200 each. Each group of patients was given one of the following four mediums: sodium iodomethamate (Neo-Iopax), 50% solution; sodium acetrizoate (Urokon), 50% solution; diatrizoate sodium (Hypaque), 50% solution; and Renografin (mixture of sodium and methylglucamine salts of diatrizoate), 76% solution. These compounds were administered in the manner prescribed by their manufacturers. Data were accumulated on the quality of the examinations produced, the incidence and types of reactions, the relative ease of administration of the mediums, and the relationship of the number of reactions to positive ocular, subcutaneous, and intravenously given tests, as well as to a history of allergy.

From the Division of Diagnostic Radiology, Montefiore Hospital (Drs. Lentino and Jacobson), and the departments of radiology, Bellevue Hospital (Drs. Zeitel and Poppel) and New York University College of Medicine (Drs. Lentino, Zeitel, Jacobson, and Poppel).

This study was aided by a grant from E. R. Squibb & Sons, New York, who supplied the mixture of sodium and methylglucamine salts of diatrizoate used in this study as Renografin.

The diatrizoate used in this study was supplied as Hypaque by Winthrop-Stearns, Inc., New York.

Mr. A. B. Siegelaub, Biostatistician, Montefiore Hospital, made the statistical analyses of the data presented.

There have been many reports in the literature describing a single urographic medium or comparing two such mediums. The results obtained by one group of investigators generally cannot be compared with those of another group. Nesbit and Lapides [1] found side-reactions in 49% of patients using a 50% solution of sodium acetrizoate. Richardson and Rose [2] found an incidence of 15% of reactions with the same drug. Lowman and co-workers [3] obtained reactions in 3.5% with a 50% solution of diatrizoate sodium, while Root and Strittmatter [4] reported 9.7% reactions. Barry and Rose [5] reported that 38% of examinations with a 70% solution of sodium acetrizoate were not diagnostic. Nesbit and Nesbitt,[6] on the other hand, obtained only 7% of unsatisfactory pyelograms utilizing the same drug. The foregoing data indicate the difficulty in evaluating results from the recent literature on urographic mediums. Other

articles dealing with this subject could be cited, but they lend no additional definitive information. We are impressed that the incidence of reactions and the grading of roentgenologic examinations are mostly subjective evaluations. The results obtained in the use of one medium by one group of observers cannot be compared with results obtained by a second group. Thus, we feel that a well-controlled comparative study of the currently used urographic mediums would be a profitable undertaking.

Technical Data

Table 1 summarizes the data supplied by the manufacturer of each of the four drugs used and shows the essential technical differences between these mediums. Each drug was administered in accordance with the instructions given by the individual manufacturer. For sodium iodomethamate, 20 cc. of the 50% solution was injected rapidly (completed within one minute). For sodium acetrizoate 25 cc. of the 50% solution was injected initially within 30 to 60 seconds, but, because of the relatively high incidence of reaction, it was felt advisable to increase the injection time to one and a half to two minutes. Some 30 cc. of 50% solution of diatrizoate sodium was injected in approximately three to four minutes, and 20 cc. of 76% solution of Renografin was injected in three minutes. In all four groups, a preliminary roentgenogram was taken before the injection, and roentgenograms were then taken at intervals of 5, 10, 15 and 20 minutes following the injection of the medium.

TABLE 1.—*Comparison of Physical and Chemical Characteristics of Urographic Mediums*

	50% Solution of Sodium Iodomethamate (Neo-Iopax)	50% Solution of Sodium Acetrizoate (Urokon)	50% Solution of Diatrizoate Sodium (Hypaque)	76% Solution of Mixture of Sodium and Methylglucamine Salts of Diatrizoate (Renografin)
% Iodine by weight	51.5	65.8	59.8	62.1
% solution used	50 (35)	50 (30, 70)	50	76
Amount of solution injected, cc.	20	25	30	20
Speed of injection, sec.	Rapid	30-60	180	180
Amount iodine injected, gm.	5.2	8.225	9.3	7.38
Specific gravity	1.335	1.335	1.3204	1.420
Basic chemical structure				

Quality of Visualization

The roentgenograms were graded according to the following criteria: (1) as "excellent," when the intensity of opacification and the degree of filling of the collecting system approached that of a retrograde pyelogram; (2) as "satisfactory," when the intensity of opacification and the degree of filling of the collecting system were sufficient to be diagnostic, but not optimal; and (3) as "unsatisfactory," when the intensity of opacification and the degree of filling of the collecting system were insufficient for a diagnostic statement. With this system of grading, the results obtained with the four urographic mediums in each of the groups of 200 patients are shown in fig. 1. A biometrically analyzed summary of the results listed in figure 1, in comparing quality of visualization of the four urographic mediums, shows that: (1) Renografin and diatrizoate sodium produced significantly more excellent and diagnostic interpretations than did sodium iodomethamate and sodium acetrizoate, with a probability of less than 0.001 (meaning that the probability of a difference this great occurring due to chance is less than 1 in 1,000, indicating a statistically significant difference); (2) Renografin and diatrizoate sodium produced approximately similar readings with no significant difference between them (probability of 0.23); and (3) sodium iodomethamate produced interpretations approximately similar to those of sodium acetrizoate (probability of 0.50).

Reactions

A comparison of the different reactions and the incidence of these reactions are given in table 2 and figure 2. In table 2 the most common reactions encountered are listed with the individual incidences and percentages. Figure 2 shows the comparative over-all incidence of reactions for the four mediums. A biometrically analyzed summary of the data in table 2 and figure 2 shows that: (1) Renografin caused significantly less reactions than the other mediums (probability of less than 0.001), and (2) sodium acetrizoate caused significantly more reactions than the other compounds (probability of 0.05). The type of reactions from sodium iodomethamate and sodium acetrizoate are apparently more unpleasant (arm pain with the former and nausea and vomiting with the latter)

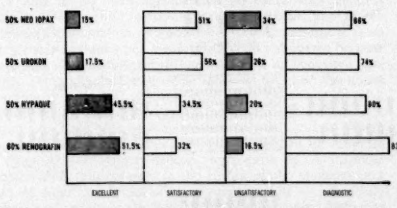

Fig. 1.—Comparison of quality of visualization of urographic mediums. Neo Iopax=sodium iodomethamate. Urokon=sodium acetrizoate. Hypaque=diatrizoate sodium. Renografin=mixture of sodium and methylglucamine salts of diatrizoate.

than the common reactions noted with the other two mediums.

Reactions in Patients with History of Allergy.—In the 400 patients given Renografin and diatrizoate sodium, an attempt made to correlate the history of allergy with the incidence of reaction showed that there were 48 patients with reactions (12.25%) and 31 with a history of allergy (17 in the Renografin series, with 3 reactions, and 14 in the diatrizoate sodium series, with 6 reactions). These data are formulated graphically in figure 3. A

TABLE 2.—*Types and Number of Side-Reactions Produced with Different Mediums* *

Reaction	Sodium Iodomethamate (Neo-Iopax)	Sodium Acetrizoate (Urokon)	Diatrizoate Sodium (Hypaque)	Renografin (Mixture of Sodium and Methylglucamine Salts of Diatrizoate)
Nausea	5	24	19	15
Vomiting	3	18	3	4
Pain in arm or site	16	10	7	2
Burning or bitter taste	2	9	5	0
Warmth, flush, chills, sweating	2	7	6	2
Pressure or palpitations	0	5	1	1
Pain in abdomen	1	4	1	0
Dizziness	2	1	5	0
Urticaria	1	1	2	0

* This represents the number of reactions in the 800 cases studied (200 patients in each group).

biometric analysis of the foregoing indicated that patients with a history of allergy showed a significantly higher incidence of reactions than did those individuals without such a history (probability of 0.002).

Testing

A special study was undertaken in a group of patients who received either Renografin or diatrizoate sodium to determine the value of various testing procedures, generally alleged to be of use in predicting reactions. The ocular test was done in 50 patients, with the reaction considered positive if at least an erythema of the conjunctiva

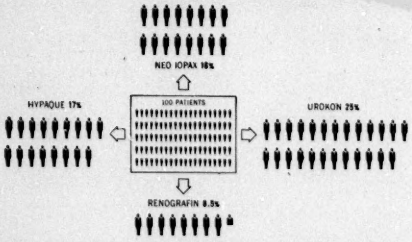

Fig. 2.—Comparative over-all incidence of side-reactions in 800 patients.

was produced. Positive reactions were seen in 10 patients, one of whom developed a reaction to the full dose of the intravenously given urographic medium. The subcutaneous test was performed in 250 patients. A reaction was considered positive if induration and erythema were noted at the site of the injection. Positive reactions were seen in 15 patients, only one of whom developed a reaction to the entire intravenous injection of the urographic medium. Intravenously given mediums were tested in 250 patients, with a positive reaction seen

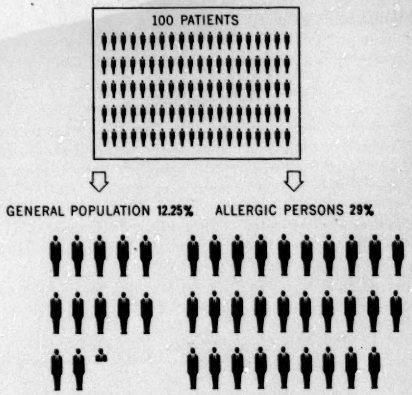

Fig. 3.—Allergy and incidence of side-reactions.

in one. In this patient (a known asthmatic), an attack was precipitated after the administration of 0.5 cc. as part of the intravenously given test. The injection was then discontinued. In figure 4 the pertinent data relating to testing and reactions are presented graphically. When these data were analyzed biometrically, no differences occurred in the incidence of reactions between those individuals showing a positive or negative skin or ocular test.

Methods of Administration

As indicated before, we followed the suggestions of the manufacturer for each individual medium regarding technique of administration (with the exception of so-

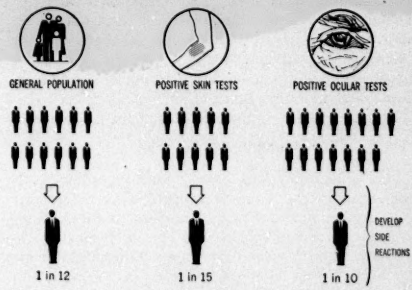

Fig. 4.—Skin and ocular testing and incidence.

dium acetrizoate). We encountered no difficulty in injecting or otherwise working with all the mediums but Renografin, which was definitely more viscous than the other mediums and required meticulous care in its administration. Scrupulous detail in warming the solution to body

temperature before use was mandatory. The Renografin solution could not be easily aspirated from the container with the same needle used for the subsequent injection, and we found it advisable to pour that medium directly into the syringe from the container or to aspirate the contents of the container through a separate large-bore needle. It is important to clean needles and syringes conscientiously immediately after use with Renografin prior to sterilization.

Summary and Conclusions

We have studied the four most commonly used intravenously given urographic mediums commercially available today. We have divided 800 patients into four groups and have administered a 50% solution of sodium iodomethamate (Neo-Iopax), 50% solution of sodium acetrizoate (Urokon), 50% solution of diatrizoate sodium (Hypaque), and 76% solution of Renografin (mixture of sodium and methylglucamine salts of diatrizoate) to each of 200 patients. The latter two offered superior results in quality of visualization, and, of these, Renografin gave the lowest incidence of reaction but was somewhat more difficult to administer because of its high viscosity. Skin and ocular testing had no value in determining reactors. Intravenous testing should be done in allergic individuals but is probably of no value in the average patient. Individuals with a history of allergy showed a significantly higher incidence of reaction to intravenously given urographic mediums as compared with the general population.

On the basis of the preceding data, the following conclusions are warranted. 1. There was no one intravenously given urographic medium that was ideally suitable for all situations. 2. Both Renografin and diatrizoate sodium produced significantly more "excellent" and "diagnostic" visualization than did the other mediums. 3. Sodium acetrizoate produced the most reactions, while Renografin caused significantly fewer reactions than all other mediums. 4. Renografin was more difficult to administer than the other three because of its high viscosity. This handicap was overcome by using a larger gauge needle, with scrupulous attention to technical details. 5. Ocular and skin testing were unsatisfactory procedures and had no value in determining whether a particular patient would develop a reaction. Intravenously given tests are probably of no value in the average patient but may be helpful in those individuals with a positive history of allergy. In such a patient, the intravenously given test is recommended solely to prevent injection with a massive dose of allergin. 6. There is a significantly higher incidence of reaction in allergic people when compared with the general population.

Since Renografin and diatrizoate sodium are considered the mediums of choice, their use in individual cases should be based on the following considerations. 1. In cases where the doctor requires ease of administration, the latter is the medium of choice. It is also preferable in a patient with thrombosed arm veins in which the dorsal wrist veins must be used, in a patient with fine antecubital veins where a fine gauge needle is necessary, or in a situation where good nursing care of needles and syringes is not uniformly available. However, the physician should realize that he obtains the convenience of ease of administration at the expense of a higher incidence of reactions. 2. Renografin is the drug of choice in all situations where incidence of reactions is the prime consideration. It is mandatory in those individuals who have sustained a reaction from a previous intravenously given urographic medium or in individuals who give a history of allergy. Because of its high viscosity, the use of Renografin requires that scrupulous technique be followed. Syringes and needles that may clog or lock must be discarded. The medium must be warmed to body temperature and preferably should be poured directly into the syringe. However, the high viscosity of Renografin may have the indirect advantage of serving as a "built-in" safety factor, since the medium cannot be forced rapidly into a vein.

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Examination of the Abdomen in Infants and Children.—Nothing is more important in the examination of an infant than evaluation of the child as a whole and such evaluation can be made only when the infant is completely disrobed. One can learn so much at a glance. Normal mental development is an important factor in evaluating abdominal tenderness. If the child has not smiled by two months of age and shows no interest in what is going on about it, one may be sure that its reactions to pain are abnormal and that evaluation of its illness cannot be accomplished according to the prescribed pattern. A six month old child who does not hold up its head, look about and wiggle must have its illness assessed differently than the alert, bright-eyed child who laughs and coos when all is well and who makes heard its objections when crossed. Is the infant acutely ill? A look at the face which has not yet learned to mask its feelings will tell you. A feeble cry, loose skin, pallor, a dry mouth, parched lips stained green at the corners with vomitus, all tell better than a spoken complaint that the infant is seriously ill. To be able to say with considerable assurance—this child is seriously ill—this child is not—is a very important part of the preliminary examination. A good light coming preferably from an angle is important when inspecting a child's abdomen because it heightens the shadows of distended bowel or abnormal peristalsis. The abdominal wall of an infant is thin and the bowel patterning of intestinal obstruction is easily observed. Parallel transverse ridges and furrows across the abdomen mean intestinal obstruction. They will be seen occasionally in cases of severe infantile diarrhea. Peristalsis from left to right in an infant is not diagnostic of pyloric stenosis, but nearly so. A scaphoid abdomen with fullness only in the region of the stomach in a 24 to 48 hour old infant who is vomiting bile is practically diagnostic of atresia of the duodenum. A suprapubic swelling at once makes the examiner suspicious of an overfilled bladder. A generally enlarged abdomen suggests Hirschsprung's disease or portal obstruction with ascites. Enlargement in either upper quadrant at once suggests Wilms' tumor or a neuroblastoma. Petechiae seen on the abdomen of a child who has abdominal pain and who has passed blood suggest Henoch's purpura and not a bleeding Meckel's diverticulum.—W. J. Potts, M.D., Examination of the Abdomen in Infants and Children, *Surgical Clinics of North America*, February, 1956.

STUDY OF FIVE HUNDRED PATIENTS WITH ASYMPTOMATIC MICROHEMATURIA

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• *Microhematuria is the occurrence of erythrocytes in the urine and is graded according to the number of cells seen in the average high-power field when the sediment from a centrifuged specimen is examined microscopically. In 500 otherwise asymptomatic patients who had this condition, the highest incidence was in the 50-59 year age group.*

The two most frequent lesions discovered when these patients underwent rigorous urologic examination were asymptomatic prostatic hyperplasia and urethritis. In some instances the lesions found were extensive and of grave prognostic import, while in 44% of the patients the urologic investigation yielded normal findings.

The study did not yield any criteria that would enable the urologist to decide which patients, in a group manifesting asymptomatic microhematuria, could safely be spared the hardship of an extensive investigation. In patients over 50 years of age such investigation appears advisable. In patients under 50 a compromise plan would consist of taking a plain roentgenogram of the urinary tract and performing a cystoscopy.

Medical literature contains numerous articles concerning the significance of gross hematuria.[1] For years urologists have pointed out the serious nature of gross hematuria and have urged complete urologic investigation of all patients with this symptom. They have stressed that the imperative need for complete urologic investigation is not diminished by the absence of other urinary symptoms or other pathological elements in the urine. Such investigation will reveal a cause for gross hematuria in a high percentage of cases. The significance of microhematuria in patients who do not have urinary symptoms, on the other hand, has received scant attention. Nevertheless, urologists, acting in consulting capacity, may be confronted with this problem several times daily. Usually a diagnostician seeks urologic advice and the consultation takes the following form. The diagnostician says, "I'd like you to see a patient who came to me because of asthma [or peptic ulcer, or hernia, or tension state, or one of a thousand medical or surgical problems. The patient may be male or female, infant, child, or adult]. He has no urinary symptoms and never has had any. His urine shows a little blood and nothing else. I've rechecked it and the blood is still there. What shall I do?" At this point the urologist is in a dilemma.

It is simple to suggest urologic investigation, but such investigation will include at a minimum excretory urography, cystoscopy, and possibly retrograde pyelography. These studies require the patient to expend time and money and to experience the pain or discomfort that accompanies these procedures. Furthermore, the urologist has the impression, from previous experience, that in the majority of cases of this type complete urologic investigation fails to reveal a significant source of the microhematuria. Thus time and effort of both patient and physician may have been spent for naught except for reassurance of them both. It is equally simple to advise that microhematuria be disregarded. The urologist, however, will be disturbed by the recollection of a patient in whom urologic investigation, performed because of asymptomatic microhematuria, resulted in discovery of a neoplasm in the urinary tract. Thus the urologist is placed between the Scylla of advising complete urologic investigation and finding nothing and the Charybdis of disregarding microhematuria and overlooking malignancy or some other significant lesion. This study was undertaken, therefore, to determine the incidence, nature, and significance of urologic lesions associated with asymptomatic microhematuria. We also sought criteria that would enable the urologist to decide whether urologic investigation was necessary and the form such investigation should take.

From the Mayo Clinic and Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

We reviewed consecutive histories of 500 patients who had undergone urologic investigation because of asymptomatic microhematuria. In each case urologic investigation consisted of excretory urography, cystoscopy, and, when indicated, retrograde pyelography. In all patients microhematuria was the only abnormal finding of urinalysis; none of the patients had past or present urinary symptoms, and neither history nor physical examination indicated the necessity of urologic investigation. Such an investigation, in most instances, was undertaken only if microhematuria was noted to persist in a second urinalysis. In men, voided specimens of urine were examined; in women, urine obtained by catheterization was employed for the second urinalysis.

Microhematuria is divided into four grades at the Mayo Clinic. Microhematuria, grade 1, exists when 1 to 8 erythrocytes are found per high-power microscopic field of a centrifuged specimen; grade 2, 8 to 30 cells; grade 3, 30 cells to three-fourths of the field; and grade 4, the entire field packed with erythrocytes. Gross hematuria is graded 5.

Results

The group of 500 patients was made up of 279 men and 221 women. The incidence of microhematuria according to decades of age is shown in table 1. It will be noted that a greater number of older patients (50 years or more) than of younger patients underwent urologic investigation because of microhematuria; this was due probably to greater incidence of microhematuria in older patients and to selection of patients for study by the

urologist. Table 2, which shows the incidence of urologic lesions according to age and sex, indicates that the incidence increases proportionate to increase in age; furthermore, lesions were found more commonly in men than in women. In table 3 the incidence of microhematuria according to grades is shown; in addition, the incidence of urologic lesions according to grade of microhematuria is noted. It may be observed that the incidence of urologic lesions is essentially the same in cases of microhematuria grades 1 to 3. The number of cases

TABLE 1.—*Incidence of Microhematuria According to Age and Sex of 500 Patients*

Age, Yr.	Total No.	Total %	Male No.	Male %	Female No.	Female %
Less than 30	11	2.2	10	3.6	1	0.5
30-39	51	10.2	28	10.0	23	10.4
40-49	134	26.8	70	25.1	64	29.0
50-59	194	38.8	102	36.6	92	41.6
60-69	98	19.6	61	21.9	37	16.7
70 or more	12	2.4	8	2.8	4	1.8
Total	500	100.0	279	100.0	221	100.0
Youngest	19 yr.		19 yr.		26 yr.	
Oldest	78 yr.		76 yr.		78 yr.	
Mean	52 yr.		52 yr.		52 yr.	

of microhematuria grade 4 is probably too small to have statistical significance. The nature and incidence of the urologic lesions are shown in table 4; in addition this table notes the incidence of the urologic lesions according to the grade of microhematuria. This table shows that about 56% of patients with asymptomatic microhematuria have urologic lesions.

Evaluation of Data

The observation that more than half of the patients had urologic lesions would appear to indicate that asymptomatic microhematuria is an ominous finding and that urologic investigation of such patients is not only advisable but necessary. However, closer study of

TABLE 2.—*Urologic Lesions in Relation to Age and Sex*

	Total	Urologic Lesions No.	Urologic Lesions %
By Age			
Less than 30	11	3	27.3
30-39	51	21	41.2
40-49	134	62	46.3
50-59	194	112	57.7
60-69	98	70	71.4
70 or more	12	10	83.3
Total	500	278	55.6
By Sex			
Male	279	174	62.4
Female	221	104	47.1
Total	500	278	55.6

table 4 indicates that this simple answer may be misleading. Examination of this table indicates a striking difference in the significance of the lesions noted, ranging from renal neoplasm to verumontanitis. Certainly, urologic investigation, instigated because of microhematuria, that leads to detection of a renal neoplasm is highly desirable. It may be questioned, however, whether complete urologic investigation is indicated in order to inform a man 60 years old, who does not have urinary symptoms, that he has verumontanitis.

We considered that division of the lesions into categories based on their significance would help clarify this problem. The following three categories were selected: (1) significant lesions, (2) moderately significant lesions, and (3) insignificant lesions. A significant lesion was defined as one that was a clear, immediate threat to the

TABLE 3.—*Incidence of Microhematuria and Urologic Lesions According to Grades*

Grade of Hematuria	Total No.	Total % *	Urologic Lesions No.	Urologic Lesions % †
1	133	26.6	73	54.9
2	191	38.2	101	52.9
3	169	33.8	98	58.0
4	7	1.4	6	85.7
Total	500	100.0	278	55.6

* Based on 500 patients.
† Based on total cases in corresponding grade.

patient's life or continued well-being or that required major surgical procedures or significantly altered the patient's way of life. A neoplasm, for example, clearly fits into this category. A moderately significant lesion was defined as one that caused slight, if any, alteration in the patient's way of life, required minor or no treatment, and appeared as a remote threat, if any, to the patient's continued well-being. A minute calculus located in a minor calyx of a kidney fits into this category. An insignificant lesion was defined as a lesion that did not require treatment, did not alter the patient's way of life, and did not appear as a threat to the patient's con-

TABLE 4.—*Nature and Incidence of Urologic Lesions and Incidence According to Grade of Microhematuria*

Urologic Lesion *	Patients No.	Patients % †	Grade of Microhematuria 1	2	3	4
	278	55.6				
Asymptomatic prostatic hyperplasia	118	23.6	22	51	43	2
Urethritis	106	21.2	35	32	38	1
Renal calculus	17	3.4	2	6	6	3
Cystitis	17	3.4	4	6	7	..
Urethrotrigonitis	16	3.2	4	7	5	..
Vesical neoplasm	9	1.8	1	2	6	..
Prostatic calculi	9	1.8	1	3	5	..
Renal cyst	6	1.2	4	..	2	..
Urethral stricture	5	1.0	2	1	2	..
Hydronephrosis	3	0.6	..	2	1	..
Renal neoplasm	2	0.4	1	1	..	..
Ureteral calculus	2	0.4	1	1	..	..
Ureterocele	2	0.4	1	1	..	..
Urethral polyps	2	0.4	1	1	..	..
Occlusion of renal pedicle (?)	1	0.2	..	..	1	..
Pyelonephritis	1	0.2	..	1	..	..
Essential hematuria	1	0.2	..	..	..	1
Horseshoe kidney	1	0.2	1	..	..	..
Renal agenesia	1	0.2	..	1	..	..
Ureterectasis	1	0.2	..	1	..	..
Pinpoint ureteral meatus	1	0.2	..	1	..	..
Vesical diverticulum	1	0.2	..	..	1	..
Verumontanitis	1	0.2	..	..	1	..
Indeterminate	4	0.8	..	1	3	..

* Since a patient may have more than one lesion, the total number of lesions will be greater than the total number of patients with lesions.
† Based on 500 cases.

tinued well-being. A mild degree of asymptomatic prostatic hyperplasia not associated with other evidence of pathological nature fits into this last category.

The task of dividing the lesions noted in table 4 into the three categories described in the preceding paragraph is more difficult than appears at first sight; for

example, urologic investigation of a patient who had microhematuria disclosed a space-occupying renal lesion. Surgical exploration established that the lesion was a simple cyst 2 cm. in diameter. Is the cyst to be considered a significant lesion that warranted urologic investigation and surgical exploration, or should the cyst be considered an insignificant lesion? Would the patient have been served just as well if investigation had not been instituted? Similarly, is a minute renal calculus, located in a minor calyx, that in the future might cause renal colic or interfere with renal function to be considered a significant lesion? Such questions are not answered easily. The following case report is an example of the difficulty in deciding which lesions are significant to the patient; it illustrates how the detection of what might be considered an insignificant urologic lesion led to the discovery of a significant extraurinary lesion.

TABLE 5.—*Nature and Incidence of Significant Lesions and Incidence According to Grade of Microhematuria*

Urologic Lesion	Patients No.	Patients % *	Grade of Microhematuria 1	2	3	4
Vesical neoplasm	9	1.8	1	2	6	..
Renal calculus	4	0.8	..	2	2	..
Renal cyst	4	0.8	3	..	1	..
Renal neoplasm	2	0.4	1	1	..	..
Ureteral calculus	2	0.4	1	1	..	..
Hydronephrosis	1	0.2	..	1	..	..
Occlusion of renal pedicle (?)	1	0.2	..	..	1	..
Urethral stricture	1	0.2	..	1	..	..
	24	4.8				

* Based on 500 cases.

A man, 64 years old, sought medical advice because of recurrent attacks of abdominal distention of four months' duration. He denied urinary symptoms. The results of routine laboratory studies and roentgenographic examinations of the gastrointestinal tract were normal or negative with the exception of those of urinalysis. Microhematuria graded 2 was noted, and urologic investigation was undertaken that disclosed a minute calculus in the lower calyx of the left kidney. The discovery of the minute calculus led to determinations of the calcium and phosphorus content of the serum; these were 11.3 and 2.4 mg. per 100 cc. respectively. These studies were repeated, with essentially similar results. Elevation of the serum calcium level and depression of the serum phosphorus suggested a diagnosis of hyperparathyroidism. This diagnosis was established by surgical removal of an adenoma of mixed cell type, which weighed 550 mg., from the right inferior parathyroid glandule.

TABLE 6.—*Nature and Incidence of Moderately Significant Lesions and Incidence According to Grade of Microhematuria*

Urologic Lesion	Patients No.*	Patients % †	Grade of Microhematuria 1	2	3	4
Renal calculus	13	2.6	2	4	4	3
Urethral stricture	3	0.6	1	..	2	..
Renal cyst	2	0.4	1	..	1	..
Hydronephrosis	2	0.4	..	1	1	..
Pyelonephritis	1	0.2	..	1	..	..
Essential hematuria	1	0.2	..	..	..	1
Horseshoe kidney	1	0.2	1	..	..	..
Renal agenesia	1	0.2	..	1	..	..
Ureterectasis	1	0.2	..	1	..	..
Pinpoint ureteral meatus	1	0.2	..	1	..	..
Vesical diverticulum	1	0.2	..	..	1	..
	23	4.6				

* Since a patient may have more than one lesion, the total number of lesions will be greater than the total number of patients with lesions.
† Based on 500 cases.

The lesions we considered significant are shown in table 5. It will be noted that a significant lesion was found in about 5% of patients who had asymptomatic microhematuria. Neoplasms were discovered in about 2% of our cases. The vesical neoplasms varied in size from small to extensive and, with a single exception, were papillary transitional cell epitheliomas graded 1 (Broders). An infiltrating transitional cell epithelioma graded 3 was observed in one instance. The renal neoplasms consisted of hypernephroma and a transitional cell epithelioma of the renal pelvis. Each patient who had a significant lesion of the urinary tract was 50 years of age or older; this observation will be referred to later.

A lesion of moderate significance was noted in about 5% of patients (table 6) and an insignificant lesion was observed in about 45% (table 7). In the latter group, in particular, it was difficult to establish a relationship between the lesion and microhematuria. Thus it could not be stated with certainty that mild prostatic hyperplasia, for example, was responsible for microhematuria. Finally, a lesion could not be found in about 44% of patients with asymptomatic microhematuria (table 8).

TABLE 7.—*Nature and Incidence of Insignificant Lesions and Incidence According to Grade of Microhematuria*

Urologic Lesion *	Patients No.	Patients % †	Grade of Microhematuria 1	2	3	4
Asymptomatic prostatic hyperplasia	118	23.6	22	51	43	2
Urethritis	106	21.2	35	32	38	1
Cystitis	17	3.4	4	6	7	..
Urethrotrigonitis	16	3.2	4	7	5	..
Prostatic calculi	9	1.8	1	3	5	..
Ureterocele	2	0.4	1	1	..	..
Urethral polyps	2	0.4	1	1	..	..
Urethral stricture	1	0.2	1	..	..	..
Verumontanitis	1	0.2	..	..	1	..
	227	45.4				

* Since a patient may have more than one lesion, the total number of lesions will be greater than the total number of patients with lesions.
† Based on 500 cases.

TABLE 8.—*Occurrence of Microhematuria Without Urologic Lesions According to Grade of Microhematuria*

Grade of Microhematuria	Patients
1	60
2	90
3	71
4	1
Total	222*

* 44.4% of 500 patients.

We sought to determine whether the incidence of significant urologic lesions was greater in cases in which microhematuria was of higher grade, that is, grade 3 or 4, than in cases in which microhematuria was of grade 1 or 2. If this hypothesis could be established, it might indicate that urologic investigation could be confined to cases in which there were higher grades of microhematuria. This hypothesis could not be established. Study of table 3 indicates that the incidence of lesions is essentially the same in cases of microhematuria graded 1, 2, or 3 (the number of cases included in grade 4 is probably too small to have statistical significance). Of more importance, however, is the fact that the incidence of significant lesions was not greater in the higher than in the lower grades of microhematuria. This fact can be exemplified by the following report, in which the most serious case in the entire series was associated with microhematuria grade 1.

A man, aged 59 years, came to the clinic because of loss of 45 lb. (20.4 kg.), "full feeling," and nausea after meals, belching, and loss of strength during the previous 18 months. Urinary symptoms were absent. His physician discovered a "defect in the pre-pyloric area" and referred the patient to the clinic. Physical examination disclosed wasting and a sense of resistance in the upper right quadrant of the abdomen. Roentgen examination revealed a polyp, less than 1 cm. in diameter, in the prepyloric segment of the stomach; direct roentgenographic evidence of malignancy was absent. Arrangements were made for gastric surgery, but inasmuch as urinalysis disclosed microhematuria grade 1 it was considered advisable to examine a second specimen of urine. Microhematuria grade 1 was noted in the second specimen, urologic studies were undertaken, and a diagnosis of hypernephroma of the right kidney was made. Surgical exploration disclosed that the kidney was replaced by a huge nodular neoplasm that extended along the vena cava. The peritoneum was opened, and nodular metastases were noted on the surface of the peritoneum. Nephrectomy was performed, and the kidney weighed 1,350 gm. Microscopic study disclosed hypernephroma with extensive involvement of the renal veins with neoplasm.

Comment

Our study failed to disclose any factors that permit the urologist to differentiate microhematuria of significant origin from that of insignificant origin; this can be accomplished by urologic investigation only. The grade of microhematuria is not decisive. Microhematuria grade 1 or 2 was noted slightly more frequently than microhematuria grade 3 or 4 in patients with significant lesions. The most malignant lesion in the entire series, an extensive hypernephroma, was found in a patient with microhematuria grade 1.

It is our belief that complete urologic investigation should be performed in all cases of asymptomatic microhematuria. This conclusion is based largely on the fact that a lesion of varying significance will be discovered in about 10% of cases and further that such investigation will permit the physician to reassure the remaining 90% of patients that the cause of the microhematuria was not significant or could not be detected. It is not difficult to recall numerous other diagnostic procedures that yield a smaller percentage of positive results.

If the urologist desires to perform urologic investigation in selected cases, there appears to be an alternate, although less acceptable, plan for the study of patients with asymptomatic microhematuria. It was noted in our study that each patient who had a significant urologic lesion was 50 years of age or older. Urologic investigation, according to this alternate plan, would consist of excretory urography and cystoscopy if the patient is 50 years of age or older, and a plain roentgenogram of the urinary tract, plus cystoscopy, if the patient is younger than 50 years. The alternate plan would, according to our statistics, permit the detection of all significant urologic lesions, more than three-fourths of the lesions considered moderately significant, and all lesions that we considered insignificant.

Persistence of microhematuria is sometimes employed to determine the necessity of urologic investigation. By this method the patient submits specimens of urine for analysis weekly or biweekly for four to six weeks. If microhematuria is noted in a majority of specimens, urologic investigation is instituted. This plan of action is based on the supposition that microhematuria is more likely to be persistent when the lesion is significant than when the lesion is of lesser significance or when a lesion cannot be detected. This supposition appears logical but has not been established as fact.

There are several possible causes for microhematuria noted in about 44% of the patients in our study in whom urologic investigation yielded normal findings. First, normal urine may contain erythrocytes. An Addis count of normal urine collected during a period of 12 hours will disclose 0 to 500,000 or possibly one million erythrocytes. Larcom and Carter [2] studied single voided specimens from 3,000 healthy men applying for employment; in 2,484 instances, urinalysis did not disclose erythrocyturia. In 2% of the group two to three erythrocytes and in 0.7% four to five erythrocytes were noted in each high-power field of the microscope. These authors concluded that the presence of more than two erythrocytes in each high-power field may indicate an increased or abnormal loss of erythrocytes from the urinary tract. Secondly, it is probable that in some instances erythrocyturia results from trauma incidental to physical examination. It is customary at the Mayo Clinic to perform physical examination prior to the patient's submission of urine for analysis. Digital rectal examination and palpation of the prostate gland and vaginal examination with palpation of the urethra are routine, essential parts of physical examination. It is possible that such examinations, even if performed gently, may give rise to erythrocyturia. Thirdly, erythrocyturia may result from subclinical urologic or other disease of the kidneys. Thus, a minute angioma of a kidney could cause erythrocyturia and defy clinical detection. Similarly, erythrocyturia may be the only manifestation of latent glomerulonephritis.

Summary and Conclusions

In urographic and cystoscopic studies of 500 patients who did not have urinary symptoms but who had microhematuria as the only significant abnormal finding of urinalysis, a lesion varying in significance from great to moderate was detected in about 10% of patients; the lesion was neoplastic in about 2% of patients. The remaining 90% of patients were divided into approximately equal groups in which either the lesion noted was insignificant or a lesion could not be detected. An unrewarding effort was made to establish criteria that would enable the urologist to select patients for urologic studies in order not to overlook significant lesions and yet not to subject each patient to extensive investigation. Lacking such criteria, it appears advisable to perform complete urologic investigation in all cases of asymptomatic microhematuria. A compromise but less acceptable plan consists of complete urologic investigation of all patients 50 years of age or older. Urologic investigation of patients younger than 50 years, according to this plan, would consist of the taking of a plain roentgenogram of the urinary tract, plus cystoscopy.

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EVALUATION OF THE SERUM GLUTAMIC OXALACETIC AMINOPHERASE (TRANSAMINASE) TEST

ITS USE IN DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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• *Serum aminopherase levels were determined in 77 patients with the unequivocal diagnosis of myocardial infarction and were compared with the levels found in 73 patients with other diseases. A strong association was found between myocardial infarction and high serum aminopherase levels.*

The occasional finding of a low aminopherase level in the undeniable presence of myocardial infarction (false negative) was explained by the occasionally transient nature of the elevation; the danger of confusion can be reduced by sufficiently prompt and frequent determinations. The finding of a high aminopherase level in the absence of myocardial infarction (false positive) was also observed, especially in disease of the pancreas and liver.

The glutamic oxalacetic serum aminopherase (transaminase) test is now being promoted by many clinical laboratories as a highly specific test in determining the presence and the extent of a myocardial infarction. The ability to positively diagnose myocardial infarction in cases in which the history is confusing or in which the electrocardiographic findings are equivocal would be a distinct improvement in patient management. It thus becomes important to evaluate the reliability of the glutamic oxalacetic serum aminopherase test in a large series of cases.

Materials and Methods

The glutamic oxalacetic serum aminopherase test was made available to the house staff of the Los Angeles County Hospital. The test was performed on 95 patients who had been given a diagnosis of myocardial infarction. Fifty-five patients without infarction but with a number of other diseases were studied in an effort to establish the specificity of the test. The standard schedule indicated five-day serial determinations. Because of the delay in arrival of some of the patients and because of the number of persons involved in drawing the tests, this was not accomplished in all cases. The history, physical examination, laboratory studies, serial electrocardiograms, ward diagnosis, and course in the hospital of each patient were reviewed independently by us without prior knowledge of the level of the serum aminopherase. The final diagnosis was a composite of these reviews.

The patients were then grouped on the basis of the final diagnosis into the categories shown in table 1. The categories are unequivocal myocardial infarction, with or without serum aminopherase elevation; equivocal myocardial infarction, with or without serum aminopherase elevation; cardiovascular problems without myocardial infarction, with or without serum aminopherase elevation; and other diseases, with or without serum aminopherase elevation. Patients in the unequivocal category are patients about whom, by history, physical examination, laboratory studies, serial electrocardiograms, and course in the hospital, there was no question in our opinions or in the ward physician's that a myocardial infarction was present. Patients placed in the unequivocal group on the basis of their serial electrocardiograms were required to have proof of tissue death. A separate review was made of those cases in the equivocal category as described below. After the final diagnosis had been made, the levels of the serum aminopherase were added to the record. A serum aminopherase level of 40 units was selected as the dividing line between normal and abnormal as suggested by LaDue and others.[1]

The serum aminopherase levels were determined by the method of Karmen and others.[2] Tests for reproducibility of the method were made on two specimens, one normal and one abnormal. The normal serum, determined 10 times in one day, showed a mean of 25.3 units with a variability of ±6.1% representing 95% limits. The abnormal serum, determined eight times, showed a mean of 88.8 units with a variability of ±6.7% for 95% limits.

Results

It will be noted that there were 77 proved or unequivocal cases of myocardial infarction in table 1. A high correlation of elevated serum aminopherase levels in patients in category 1, in whom the diagnosis of myocardial infarction was a certainty, is demonstrated. In the group having proved infarcts, there were 22 deaths; in 7 of these cases autopsy was done.

The most important categories, however, that must be considered are those that contain persons with apparent false-negative or false-positive diagnoses. Category 2 lists those patients who had unequivocal evidence of myocardial infarction and who did not have abnormally elevated serum aminopherase levels. The breakdown of these persons with apparent false-negative diagnoses reveals that this group is comprised principally of those persons inadequately studied. In 5 of the 14 persons with false-negative diagnoses the series of determinations was begun three or more days after the probable date of infarction; 6 additional patients from this group

From the Los Angeles County Hospital services of the departments of medicine of the University of Southern California and the College of Medical Evangelists (Drs. Denney, McAuley, Martin, and Ware) and the Bioscience Laboratories (Dr. Segalove).

This study was supported in part by a grant from the Attending Staff Association of the Los Angeles County Hospital.

Electrocardiographic tracings in the equivocal categories were reviewed by Dr. William Paul Thompson.

had but a single determination of serum aminopherase level. Three patients, however, had unequivocal evidence of myocardial infarction and only normal serum aminopherase levels. Close scrutiny of these cases fails to reveal any apparent reason for the discrepancy. This group constitutes 4.75% of the cases of proved myocardial infarction.

TABLE 1.—*Grouping of Patients With and Without Myocardial Infarction Used to Establish Specificity of Test*

Category	Patients, No.
1. Unequivocal myocardial infarction with high serum aminopherase level	63
2. Unequivocal myocardial infarction with low serum aminopherase level	14
3. Equivocal myocardial infarction with high serum aminopherase level	12
4. Equivocal myocardial infarction with low serum aminopherase level	6
5. Cardiovascular problems (without recent myocardial infarction) with high serum aminopherase level	8
6. Cardiovascular problems (without recent myocardial infarction) with low serum aminopherase level	27
7. Other diseases with high serum aminopherase level	12
8. Other diseases with low serum aminopherase level	8
Total	150

Categories 3 and 4 (table 1) are principally comprised of patients in whom myocardial infarction was strongly suspected. In these patients proof was lacking, often due to the presence of previous infarction or the presence of left bundle-branch block. These categories, termed equivocal, also include those patients over whom there was disagreement on the final diagnosis among us or between us and the ward physicians or cases in which neither we nor the ward physicians felt able to conclusively state that an infarct was or was not present. These categories constitute the greatest areas of potential usefulness of the test and yet, by their very nature, are the categories from which no conclusions can be drawn at this time. Seventeen patients fell into these categories; 12 patients had abnormally elevated serum aminopherase levels.

Glutamic oxalacetic serum aminopherase tests were made in 35 patients with other cardiovascular diseases and without evidence of myocardial infarction. Twenty-seven of these patients had low serum aminopherase level, while eight had a high serum aminopherase level. Four cases of pulmonary embolism divided equally between the two groups. Five cases of acute pericarditis, however, fell consistently into the group with low serum aminopherase levels. Included in the group with low serum aminopherase levels (less than 40 units) were two cases of angina pectoris or coronary insufficiency; six of old myocardial infarction with angina pectoris; seven of hypertensive heart disease with congestive failure; four of rheumatic heart disease (two with congestive failure); one of congestive failure (etiology unknown); one of rheumatic heart disease with probable pulmonary embolism; and one of pulmonary embolism. Included in the group with high serum aminopherase levels (more than 40 units) were the following eight cases: one of diabetes mellitus, with probable pulmonary embolism, pleural effusion, and hemoptysis; one of rheumatic heart disease, with congestive failure and infarcts of liver, spleen, and kidney at autopsy; one of hypertensive heart disease, with congestive failure and pneumonitis; two cases of angina pectoris; one of hypertensive heart disease and probable pulmonary embolism; one of organic heart disease (etiology unknown), with congestive failure, hepatosplenomegaly, and hyperuricemia; and one of rheumatic heart disease, with mitral stenosis and insufficiency, auricular fibrillation, and congestive failure.

In category 7 are those patients with other diseases in whom the serum aminopherase was tested (table 2). The occurrence of high serum aminopherase levels in jaundiced patients is well known. The presence of high serum aminopherase values in pancreatitis has not previously been described. The highest serum aminopherase level of the series, 16,540, was found in a case of acute hemorrhagic pancreatitis. Because of this finding, 10 patients with pancreatitis were studied; half of these patients had abnormally elevated serum aminopherase levels.

Comment

Elevation of the level of serum glutamic oxalacetic aminopherase in patients with myocardial infarction was observed by Nydick and others.[3] They also report high values in jaundice and low values in pulmonary infarction. They report one possible false-negative case. Rudolph has reported on 39 patients with myocardial infarction who had elevated serum aminopherase levels,[4] and 7 false-negative cases were reported. Four of the false-negative cases came under observation after 48 hours had elapsed, and one patient died within 3 hours of infarction. Two cases were apparently true false negatives; however, 5 of 10 patients given a diagnosis of coronary insufficiency had peak levels above normal.

In determinations in experimental animals, Merrill and others[5] demonstrated that the concentration of aminopherase was lower in the infarcted myocardium than in the adjacent normal myocardium. Agress and others[6] believe that the serum aminopherase level will probably provide a roughly quantitative estimate of the amount of infarcted myocardium. Rudolph and others[7] ligated renal, splenic, mesenteric, and pulmonic vessels in experimental animals and found elevation of the serum aminopherase level after each procedure.

TABLE 2.—*Patients with Diseases Other than Cardiovascular with High and Low Serum Aminopherase Levels*

Level Over 40 Units		Level Under 40 Units	
Diagnosis	Patients, No.	Diagnosis	Patients, No.
Primary liver disease	3	Diabetic gangrene	1
Metastatic tumor to the liver	2	Metastatic tumor to the liver	1
Acute pancreatitis	5	Acute pancreatitis	5
Diabetes, fractured hip, wound abscess, and transfusion reaction	1	Gastrointestinal bleeding and urinary tract infection	1
Diabetic acidosis, pancreatitis, and pneumonia	1		

The results of the current study indicate that the elevation of the glutamic oxalacetic serum aminopherase level is highly suggestive of myocardial necrosis if the presence of other types of tissue necrosis and of liver disease or jaundice can be excluded. Elevation of the serum aminopherase level in half of the cases of acute pancreatitis and in half of the cases of pulmonary embolism is disappointing in that these diagnoses are not infrequently entertained in the differential diagnosis of myocardial infarction. In an attempt to discover another

form of tissue necrosis that could elevate the serum aminopherase level, a diabetic patient with gangrene of a lower extremity was tested without finding serum aminopherase elevation.

Serial determinations are necessary. Tests should be begun as soon as possible after the infarction. The rise in level may be transient. Return to normal may occur within 36 hours. The serum aminopherase level may remain elevated as long as 14 days after a single clinical episode of infarction but usually falls to normal levels in 3 to 5 days. The height of the serum aminopherase level appears to bear a rough clinical correlation to the severity of the infarction. The average maximum rise took place on the second day after infarction, although in 12% of the cases the time of maximum rise was after the third day.

A special range of usefulness seems likely to be found in patients who have angina pectoris or coronary insufficiency, pericarditis, bundle-branch block, or previous myocardial infarction with a suggestive recent history. Until this category can be enlarged and the validity of any conclusions strengthened by an accumulation of autopsy data, this remains speculative.

Summary

The glutamic oxalacetic serum aminopherase (transaminase) test was performed on 95 patients with proved or suspected myocardial infarction and on 55 patients with other diseases. Three false-negative results were found in patients with unequivocal myocardial infarction, an incidence of 4.75%. False-positive results were found in certain other types of tissue necrosis. These included some cases of liver disease, jaundice, acute pancreatitis, and pulmonary embolism. The glutamic oxalacetic serum aminopherase test appears to have a definite place in the diagnosis of acute myocardial infarction; however, more determinations need to be made in the equivocal categories.

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USE OF METHALLENESTRIL (VALLESTRIL) IN CONTROL OF MENOPAUSAL SYMPTOMS

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• *Menopausal symptoms were treated by administering 6 mg. of methallenestril (a synthetic estrogen) daily to a test group of 100 women; a contratest group of 20 women received a placebo. Relief of symptoms was obtained in 91% of the test and 15% of the contratest group.*

This subjective evidence was corroborated by the objective findings in vaginal smears taken from certain patients. An estrogenic response appeared after 10 to 14 days of this medication and persisted for 16 to 30 days after medication was stopped. The dosage used did not cause withdrawal bleeding or any other untoward effects but generally gave a feeling of well-being. A warning against unnecessarily prolonged medication is offered; periodic interruption to observe the results will determine whether additional therapy is required.

It is the purpose of this report to record observations made over a two-year period on the value of methallenestril (Vallestril) in the control of climacteric symptoms. The study was controlled by employing an identical placebo. Much has been written in recent years about the management of patients in the menopause, and most authorities agree [1] that they are best served by care that is as conservative as possible. We are in agreement with this principle of conservatism.

The symptoms presented by these patients are mainly those of vasomotor irritability and regressive changes in tissues derived from the Müllerian duct system. Most women require no medication in bridging this period of their life, although many require explanation and reassurance. Some, whose symptoms are more severe than those of the majority, will require temporary substitutive estrogen therapy in addition to such psychological care as is indicated in the individual patient. The disadvantage of many of the available estrogens is centered about the appearance of some incidence of nausea, edema, or withdrawal bleeding. For this reason an estrogenic agent that will control the symptoms of the menopause without these disadvantages should be of considerable value. This type of activity has been claimed for methallenestril, and our study supports the claim.

Methallenestril is a single, crystalline chemical substance with estrogenic activity but with a low incidence of undesired actions. Its descriptive formula is 3-(6-

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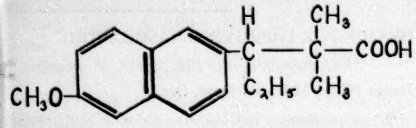
The methallenestril used in this study was supplied as Vallestril by Dr. J. William Crosson, of G. D. Searle & Co., Chicago.

methoxy-2-naphthyl)-2, 2-dimethylpentanoic acid, and its structural formula may be shown as follows:



It is weakly acidic in reaction and is relatively insoluble in water and gastric contents but soluble in alcohol, oil, and dilute bases such as occur in the intestinal secretions. When administered in an oily solution to castrated female rats, a highly keratinized vaginal epithelium can be demonstrated,[2] and this keratinization persists for several days; however, methallenestril exerts a minimal proliferative activity on the endometrium when administered to immature female mice by the Rubin technique.[2a]

Method of Study

Patients studied in this series consisted of 85 from the gynecologic endocrine clinic of the New York Medical College and 15 from our private practice. They ranged from 35 to 62 years of age, with 20 patients between the ages of 35 and 40, 28 between 41 and 45, 39 between 46 and 50, 9 between 51 and 55, and 4 over 55. All patients were given a thorough physical examination, and those manifesting evidence of pelvic abnormality were rejected as unsuited for this study. Each of those included had been amenorrheic for at least six months. No differentiation was made between patients undergoing artificial and physiological menopause. Repeated vaginal smears were taken from a sufficient number of these patients to determine the activity of methallenestril in producing an estrogenic response in the exfoliated cells of the mucosa.

The dosage schedule of methallenestril used was 6 mg. (two tablets) daily for 30 days. Medication was then interrupted for two weeks and the need for a second course determined by the return or absence of symptoms. No patient was given more than three such courses of treatment in any four-month period. To control the study and to provide a reference standard, 20 patients were given a placebo tablet indistinguishable from the medicament. These patients met the same standards for inclusion in the study as did those receiving methallenestril.

Results

The effect of medication on menopausal symptoms in these patients was determined of necessity by evaluation of subjective manifestations. Objective evaluation of estrogenic activity of the drug was determined by study of vaginal smears and by endometrial biopsy. The effect on menopausal symptoms was rated as good if, after two weeks of therapy, more than 75% of the symptoms had subsided and if they remained in remission for an additional period of four weeks. A poor response was one in which there was less than a 50% reduction in symptoms. The results obtained in our studies as determined by these ratings of effectiveness are shown in the table.

In contrast, of the 20 patients in the control group who received placebos, only one patient had good results while 2 had only fair results and 17 had poor results. Thus, relief of symptoms was observed in 91% of the patients treated with methallenestril but in only 15% of those receiving placebos.

It is important to accent that none of the patients treated with methallenestril developed untoward reactions of any kind; no instances of withdrawal bleeding were encountered. Another observation that was considered remarkable was the report of a feeling of well-being noted by almost all of the patients who responded to the medicament.

In order to provide an objective measure of estrogenic activity, weekly vaginal smears were taken from certain of the patients throughout their period of medication and for several months after cessation of therapy. The smears were stained as a wet preparation according to the recommendations of Rakoff [3] and studied immediately in the clinic. This procedure offers the advantage of providing immediate information concerning estrogenic effect. In addition, dosage can be adjusted according to the epithelial response, since quantitative changes are manifested in the vaginal cytology. The not inconsiderable disadvantage of this procedure centers about

Results of Methallenestril Medication on the Subjective Symptoms of the Menopause

Age	Patients, No.	Results		
		Good	Fair	Poor
35-40	20	17	2	1
41-45	28	23	3	2
46-50	39	32	5	2
51-55	9	5	2	2
Over 55	4	1	1	2
Total	100	78	13	9

the fact that, because it is a wet-slide technique, a series of specimens cannot be accumulated for later comparative study; however, it was our observation that, in the dosage used, methallenestril showed an estrogenic response in the vaginal cytology that appeared 10 to 14 days after institution of therapy. This response, which was slight, persisted for 16 to 30 days after discontinuance of therapy with the medicament.

As already noted, no instance of withdrawal bleeding was encountered in our series of patients treated with methallenestril. This characteristic of the drug is of considerable importance to the clinician and eliminates a source of worry and annoyance to the patient as well as periods of explanation by the physician. In order to test further the activity of the drug on the endometrium, additional studies were undertaken. Three patients were selected who were scheduled for hysterectomy for reasons not considered to influence the activity of the drug. Endometrial biopsy specimens were obtained for control purposes, after which 100 mg. of methallenestril was administered. Three days later, the scheduled hysterectomy was performed and additional endometrium specimens were taken for comparison with the controls. These heavy doses of methallenestril produced a slight proliferation, but, in general, little effect was noted. This series of special studies is being continued.

Comment

The management of the symptoms associated with the climacteric is a subject currently receiving considerable attention. Its relationship to the physiological and psychological process of aging is of great importance. Most patients will not require medication in bridging this period of waning ovarian function, and only reassurance will be required; however, in those instances where active therapy is needed, close attention to the patient's history and physical findings is essential. It is our opinion that estrogenic substitutive therapy should be withheld from women who have a strong family history of breast or fundal carcinoma. In addition, we believe that estrogens should not be prescribed when patients have pathological pelvic conditions.

Those patients who meet the requirements we have outlined should receive estrogenic therapy; our observations revealed good or fair results in 91% of 100 patients treated with methallenestril and in only 15% of 20 patients treated with placebos. In addition, most physicians are well aware of the anxiety caused a patient when bleeding occurs; for this reason, as well as the possibility of masking carcinoma, the great advantage of methallenestril lies in the absence of bleeding during therapy or on discontinuance of treatment with this drug. As is usual with all estrogens, the warning against unnecessarily prolonged medication is offered. Estrogens are known to suppress anterior pituitary function, and, consequently, their administration should be interrupted periodically to determine whether additional therapy is required.

Summary

One hundred patients were observed to determine the usefulness of methallenestril (Vallestril) in controlling menopausal symptoms. A control group of 20 patients was given identical-appearing placebo tablets. Relief of symptoms was observed in 91% of the patients treated with methallenestril and in only 15% of those receiving placebos. No withdrawal bleeding or other untoward effects were noted in the patients receiving methallenestril. Typical estrogenic cytological effects were found in vaginal smears 10 to 14 days after institution of methallenestril therapy; this effect continued for 16 to 30 days after cessation of therapy. A feeling of well-being was noted by the patients who responded to therapy.

11 E. 87th St. (Dr. Goldfarb).

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CLINICAL NOTES

DEVICE FOR IMPROVING NASOGASTRIC SUCTION

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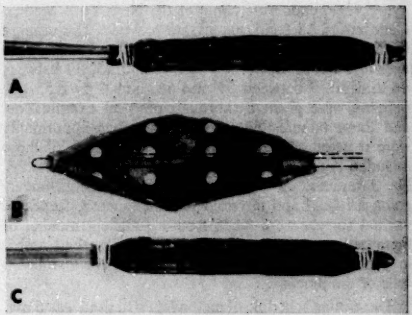
While continuous nasogastric suction is perhaps less frequently employed than formerly, there are occasions when its effectiveness is of critical importance. One cause of its occasional failure appears to be due to the tendency of gastric mucosa to obstruct the openings in the gastric end of the tube. This has been noted with the use of the standard-type water displacement suction and with the intermittent mechanical suction, when the latter apparatus is acting through the usual 1 gal. trap bottle. The negative pressure in the trap bottle maintains, in effect, constant suction. Increasing abdominal distention has been observed in spite of the best efforts to maintain gastric aspiration.



A, polyethylene tube for sump drainage effect. *B*, with basket split open to show inside projections for maintaining clearance. *C*, basket tied to 14 F. Levin tube. Ends of tube are molded to fit external diameter of Levin tube; apertures in basket are same diameter as inside of Levin tube; and thickness of wall is 1/64 in., while clearance between tube and basket is 1/32 in.

The use of reduced suction (1 cm. Hg) by shunting a simple suction breaker in the suction line has been helpful. This requires the use of one of the mechanical types of suction pumps. Soft rubber fins glued to the tube to help keep the mucosa from the openings have been tried and seemed effective but were inconvenient to prepare. The soft rubber basket illustrated has proved satisfactory. It slips over the end of a 14 F. Levin tube and is tied in place with no. 20 cotton thread. When true sump-type drainage is necessary, a polyethylene tube, size I.D. 0.062, can be introduced (see figure, *A* and *B*). This we have used in decompressing proximal distention in acute mechanical intestinal obstructions. The Levin tube is more readily passed with the basket attached. The measurements are as shown in the figure, *C*. The basket is cast of pure gum rubber and can be detached, cleaned, and used repeatedly. Two years' use of this rubber basket has shown its effectiveness in improving continuous nasogastric suction.

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NEW ADAPTATION TO THE STANDARD THREE-WAY STOPCOCK

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The standard three-way stopcock is valuable in present-day anesthesia, as it permits administration of fractionating doses of thiopental (Pentothal) sodium, relaxants, and fluids intravenously through a single venipuncture. The principle disadvantage is that there is no

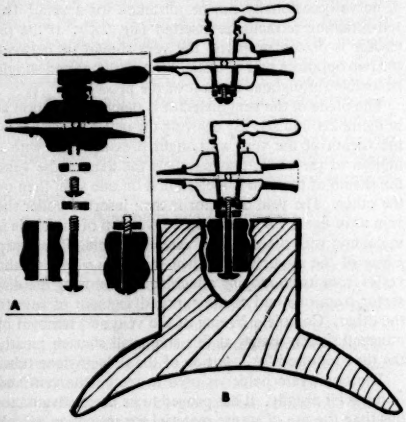

Fig. 1.—The three-way stopcock. *A*, cross section. *B*, the new adaptable parts.

stability to the syringe, and the incidence of syringe breakage is quite high. We have been able to replace the screw at the base of the selecting directional faucet with a long screw and a cylindrical washer. This is introduced into a suction rubber stopper that can be applied to any

Fig. 2.—The new stopcock in use.

flat surface. The latter keeps the stopcock firmly secure and gives stability to the syringe. We find it both practical and more economical than the various syringe holders found at present on the market.

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VENOSTOMY, AN IMPROVED "CUT-DOWN" PROCEDURE IN INFANTS AND CHILDREN

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and
Lloyd E. Harris, M.D., Rochester, Minn.

Adequate fluid and electrolyte therapy is essential in the treatment of infants and children. Although ordinary venoclysis and hypodermoclysis will often suffice, it is frequently necessary to secure a more dependable route for the administration of fluids, blood, electrolytes, and medicines. Many techniques for inserting a cannula into a vein have been described, but, although these techniques have been satisfactory, we believe that the procedure can be improved. The method we use facilitates the introduction of a polyethylene tube into a vein. The procedure is usually referred to as "cannulation" technique,[1] "cut-down" procedure,[2] or venesection,[3] but none of these terms seem to supply the correct description. We believe that the name "venostomy" is more appropriate,

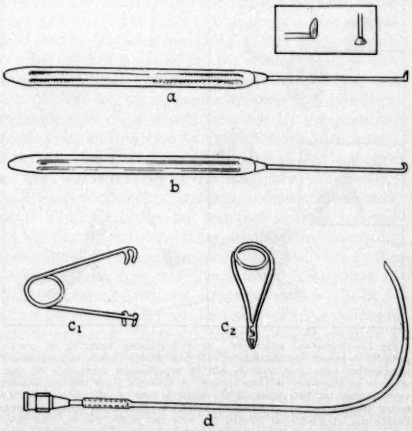

Fig. 1.—Venostomy instruments. *A*, vein dissector (inset shows dissector blade in different views). *B*, vein holder. *C*, self-retaining retractor. *D*, assembled polyethylene tube and 20-gauge needle hub. Point of polyethylene tube has short bevel to aid in insertion into incision of vein.

and we shall use this term in our discussion.

Venostomy is indicated when veins are difficult to find for venoclysis, when the child is being prepared for operation,[2b] when emergency situations exist, such as shock or peripheral circulatory collapse, and when intravenous therapy is predicted for an extended period. Three new instruments, originally produced in the section of engineering of the Mayo Clinic, have been designed for use in performing the procedure (fig. 1). The veins most commonly used for venostomy are the vena saphena magna anterior to the medial malleolus of the tibia, the vena basilica and vena mediana cubiti of the arm, and the venae metacarpeae dorsales of the hand.

From the Section of Pediatrics, Mayo Clinic and Mayo Foundation. The instruments shown in figure 1*A*, *B*, and *C* are now manufactured by the Rochester Products Company, Rochester, Minn.

If the vein to be used is located accurately, only a small incision is necessary. Constriction of the extremity by means of a tourniquet applied with moderate tension proximal to the site chosen for venostomy should cause sufficient distention to make the vein palpable or visible. Marking the position of the vein with ink or scratch marks will indicate the proper site of incision. After the site has been found and marked, the tourniquet should be removed. In emergency situations in which speed is essential and visualization or palpation of the vein difficult or impossible, the first attempt should be to use the vena saphena magna anterior to the medial malleolus because of its constant location.

Venostomy can be performed in the cubicle or room occupied by the young patient. The skin at the site of incision is prepared by washing with soap and water, followed by cleansing with one of the usual germicidal substances. The extremities of the patient should be restrained by tying them to the side of the bed or table. The extremity chosen for venostomy should be securely

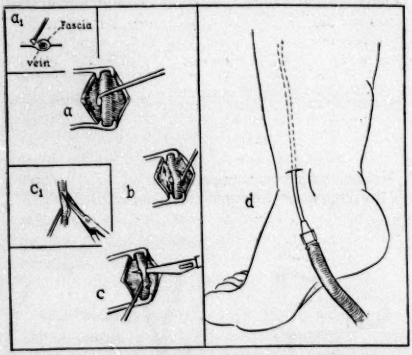

Fig. 2.—Venostomy procedure. *A*, self-retaining retractor in correct position to permit visualization of vein and dissector blade incising sheath surrounding vein. This incision will be repeated on other side of vein. A_1, view of above step in cross section. *B*, dissector blade inserted beneath vein through the two incisions of sheath in step *A*. Entire vein is dissected free by motion of dissector blade. *C*, incision of vein. A Bard-Parker no. 11 blade has pierced the vein and blade will be withdrawn toward the vein holder to cause a v-shaped nick. C_1, a v-shaped nick made in the vein with ophthalmic scissors (sharp-sharp) as indicated. *D*, relative position of foot, incision, and plastic tubing when vena saphena magna anterior to medial malleolus of tibia is used.

taped to a padded board or sandbag to restrict motion and to prevent contamination of the wound. Care should be taken to apply tape firmly enough to restrict motion, yet not so tight as to prevent venous flow. Application of adhesive tape to the joint proximal to the venostomy site may hinder passage of the polyethylene tube and therefore should be deferred until the plastic tube has been inserted the desired distance. The site of incision should be repainted with disinfectant and draped.

With a 2-cc. syringe and a 25-gauge hypodermic needle, sufficient 1% solution of procaine hydrochloride is injected just beneath the skin immediately over the vein to cause elevation of the skin over an area approximately 1 cm. in diameter. This injection serves two purposes: it causes the skin to become separated from the underlying vein, which reduces greatly the possibility of injury to the vein by the subsequent incision, and it permits a bold incision to be made in one stroke completely through the skin. The incision that is made while the skin is elevated, that is, before the solution of procaine hydrochloride is absorbed, should be transverse to the long axis of the vein and not more than 5 to 6 mm. in length. If location of the vein is inaccurate, extension of the incision laterally may be necessary.

The point of a mosquito forceps is inserted into the incision and opened to spread the skin and subcutaneous tissues. The vessel may be visualized at this point. The vein sought for is of relatively large size, and, therefore, tiny veins, which may be encountered, should be ignored. A nerve occasionally can be mistaken for a vein. The self-retaining retractor is inserted (fig. 2*A*). If the retractor is placed properly, the vein should lie between the two opposing pair of teeth of the retractor and should be visible throughout the rest of the procedure.

The blade of the vein dissector is placed in position as in figure 2*A* and A_1. By drawing the cutting edge across the sheath of the vein with slight pressure, and with a motion of the blade that parallels the axis of the vein, the sheath of the vein is incised first on one side, then on the other. The vein dissector is then inserted under the vein as in figure 2*B* so that the convex top of the blade is in contact with the undersurface of the vein. The sharp edges of the dissector are then in position to free the vessel from its underlying attachment by moving the dissector from one end of the exposed segment of vein to the other. Complete freeing of the vein and removal of attached sheath tissues at this stage will shorten greatly the time required for insertion of the polyethylene tube.

The blunt vein holder is used to secure the vein and to retract it distally. It has proved to be more advantageous than the use of suture material for retraction, which gives no positive control of the position of the vein. While the vein is held in position with the vein holder, an incision is made in the vein to cause a V-shaped nick, either with ophthalmic scissors (sharp-sharp) (fig. 2C_1) or the point of a no. 11 Bard-Parker blade (fig. 2*C*). Flow of blood or visualization of the lumen indicates that the incision is through the wall of the vein.

The needle hub and polyethylene tube of appropriate size have been assembled and beveled previously (fig. 1*D*). A size 90 polyethylene tube has been found small enough to insert in most veins and large enough to permit free passage of blood. This unit should be washed with sterile sodium chloride solution and placed in an available position close to the field. The tubing is inserted carefully into the vein for a distance of 4 to 10 cm. No sutures or ligatures are placed routinely around the vein or the polyethylene tube. In the event that the polyethylene tube cannot be inserted more than 2 cm., one ligature of absorbable surgical suture may be placed around the vein and tube to prevent accidental dislodgment.

Blood for analysis or culture may be withdrawn before the fluids are administered. The position of the tube may need to be adjusted and the rate of flow regulated. At the conclusion of the procedure the retractor and drapes are removed. The skin and subcutaneous tissue are not sutured. A sterile dressing is applied firmly to promote

hemostasis and to prevent contamination. The needle hub and the entire external length of polyethylene tube are anchored to the contour of the foot and restraint board with adhesive tape. Adequate anchorage of the polyethylene tube will permit transportation of the patient without resultant kinking or removal of the tube.

The vessel is not sacrificed because it is not ligated or divided, and it therefore remains available for future use if necessary. If irritant infusion has not caused thrombosis of the vein, it is possible to carry on prolonged intravenous therapy by the alternate use of two venostomy sites. If reinsertion of the plastic tube in a cephalic direction is attempted unsuccessfully, the plastic tube may be inserted in a caudal direction. Because no sutures are placed in the skin or subcutaneous tissue, the frequency of infection of the venostomy site is reduced and foreign-body reaction, with extrusion of suture material, is eliminated. Adequate preparation of the skin and the use of a small incision aid in the reduction of wound infections and excessive scar formation. The method described simplifies the exposure of a vein for venostomy. As one becomes more familiar with the technique of this method of venostomy, the incision-to-bandage time will approach two minutes.

Apparatus and Equipment

The nonsterile equipment needed for venostomy is as follows: tourniquet, restraints, padded board or sandbag, adhesive tape, soap and water, disinfectant, tubing for intravenous use, flasks of infusion solution, floor standard, and floor lamp. The sterile venostomy tray should include: gloves and powder; four drapes or towels; four small towel clips; 10 pieces of 4 by 4 in. absorbent gauze; one 25-gauge and one 20-gauge needle; one 19-gauge, one 20-gauge, and one 21-gauge blunt needle hub 1.5 in. long; a size 90 polyethylene tube 14 cm. long; two ampuls of 1% solution of procaine hydrochloride; one ampul of sodium chloride solution; file; scalpel; one 2-cc. and one 10-cc. syringe; one container of size 4-0 absorbable surgical suture; two pairs of mosquito forceps; a self-retaining venostomy retractor; one vein dissector; one vein holder; ophthalmic scissors (sharp-sharp); and Bard-Parker handle and no. 11 blade.

Summary and Conclusions

An improved method for venostomy emphasizes adequate preparation of the skin to prevent infection; accurate location of the vein to permit smaller incisions; the use of a self-retaining retractor to aid in visualization of the vein; careful dissection of the vein to facilitate the insertion of a polyethylene tube; and the fact that absence of skin and subcutaneous sutures and vein ligatures allows repeated use of the vein, eliminates later extrusion of sutures, and hastens healing of the incision site.

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FOOD PUMP

NEW APPROACH TO TUBE FEEDING

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John J. Prendergast, M.D.
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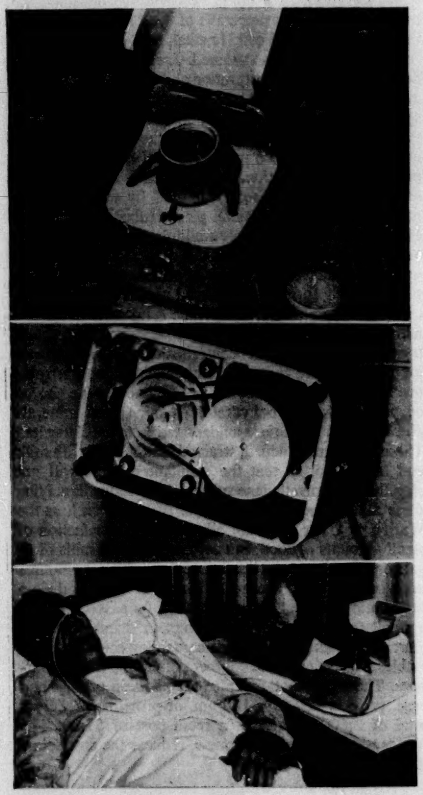
As the result of a unique cooperative effort by the medical and engineering staffs of the Chrysler Corporation and the Henry Ford Hospital, a sturdy, dependable food pump has been designed. Increasing emphasis is being directed to the restoration and maintenance of fluid and nutritional balance in every branch of medicine. In spite of the great advance in alimentation intravenously, there are few who will disagree that the oral route is preferable where it can be used. The problem is that many patients whose nutritional requirements are urgent cannot or will not take sufficient food by mouth. Fortunately, in recent years small plastic tubes have become available that are extremely well tolerated and in almost every case can be passed to the desired position in the upper gastrointestinal tract.[1] A prolonged trial of prepared feeding formulas convinced us that it was difficult to equal, much less to surpass, the results obtained with natural foods, such as milk, eggs, meat, vegetables, and fruit. Whole foods, in contradistinction to synthetic preparations, are quite well tolerated by the gastrointestinal tract and provide an ample, inexpensive source of protein, fat, carbohydrate, vitamins, and minerals plus any other heretofore unidentified essential elements.[2] These foods are liquefied, strained, and diluted with milk and fruit juice, so that the resultant mixture will not clog the fine polyethylene tubes. Methods for liquefying these natural foods are available. Blenders, such as the Waring or Oster type, are adequate for liquefaction of small amounts of food, but serum or colloid mills of 5-gal. or 20-gal. capacity are necessary if large amounts must be prepared. These mechanical devices produce a preparation of a consistency that can be passed through a small tube of less than 2.5 mm. in diameter. Commercially strained baby foods containing meat and vegetables are also excellent sources of material for this purpose. These preparations, plus the addition of milk and eggs, provide well over 180 gm. of protein and yield a total of 2,600 calories at a retail cost of $1.80. The blender or serum mill, of course, reduces the cost below the figure quoted.

Early in our work with tube feeding we became convinced that a mechanical pump was almost a necessity. The prepared material must be given at slow constant rates in elderly patients, in those critically ill, and in those for whom duodenal or jejunal feeding is necessary. Also, it is almost impossible to drip thicker preparations through small plastic tubes. Moreover, when a pump is used the patient can sit up, lie down, or turn on either side without disturbing the rate of delivery. This is an important factor in hospitals and in the home, where there is often insufficient help to make the necessary adjust-

Associate in Surgery, Henry Ford Hospital (Dr. Barron); and Retired Medical Director (Dr. Prendergast) and Medical Director (Dr. Jocz), Chrysler Corporation.

ments required by every change in position when the drip method is employed. It is absolutely imperative to control the rate of delivery because nausea, vomiting, cramps, and diarrhea can be produced with any preparation, including water, if it is given too rapidly. After experimenting with small home-made pumps that lacked the desired sturdiness, durability, and accuracy, the problem was placed before the development department of the Chrysler Corporation. After repeated tests, a pump that has given dependable service was designed (see figure, *A*). Some of these pumps have been in almost continuous 24-hour use for three years, thereby attesting to their dependability. The basic principle of the pump, i. e., that of a metal roller passing over a fixed length of rubber tubing, is not new since it was described in this country over 100 years ago; however, to our knowledge this is the first time that the principle has been applied to the production of a dependable pump to deliver liquefied natural foods through small plastic tubing. The engineers of the Chrysler Corporation insisted that only modern design and highgrade materials, including the motor bearings, would stand up under prolonged heavy duty use. An additional important feature is that these pumps are so noiseless in operation that a signal light is provided to indicate that the motor is running. These light, compact pumps are contained in a case provided with a handle to facilitate their carrying in the hospital or at home. A pulley arrangement and adjustable belt drive regulate the speed of delivery (see figure, *B*). A slow rate of delivery requiring at least six to eight hours per liter is recommended. Standard rubber latex tubing that will last for several weeks or longer is used; however, we have found that a weekly change of tubing is advisable.



Food pump. *A*, front view of pump with cover raised. Rubber tube can be readily changed. *B*, belt drive, which can be easily adjusted. *C*, pump in use. Delivery rate remains the same, regardless of patient's position. Food bottle is usually placed in a pan of cracked ice.

Electrophoretic and electrolyte changes in the blood were studied in many of the seriously ill patients who have been fed by the use of these pumps (see figure, *C*). These determinations were carried out in the Chrysler Corporation medical department [3] and have indicated quite well that this feeding program is a valuable procedure.

Conclusions

We believe that the oral route for supplementary feeding is the most preferable method. Liquefied whole food is an excellent medium for supplying additional caloric intake. The best results are obtained when the food preparation is delivered at a constant rate of speed, and we believe that a food pump is a necessity to achieve this purpose. We have designed such a pump, some of which have been in operation for three years, thereby attesting to their dependability.

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Acclimatization to High Altitude.—Less than fifty years ago serious doubts were voiced that man could survive a night spent at 20,000 feet, or climb above 23,000 feet. Each decade has pushed this limit higher and higher until now, with the highest mountain on earth climbed, it is known that well acclimatized men can reach 28,250 feet without supplementary oxygen, and can probably climb even to the summit of the earth, 29,140 feet, breathing only the ambient air. But one should note the word "acclimatized"—it is crucial. For if a man were taken suddenly to the summit of Everest from sea level he would have only a few minutes of consciousness, and he would be dead in less than ten minutes. Even if whisked suddenly to only 25,000 feet he would have less than ten minutes of consciousness, and only twenty or thirty minutes of life. Yet, at that altitude, men have lived for ten days and longer, thanks to the marvelous adaptive power of the body. Seven companions and I spent ten long days, storm-bound above 25,000 feet, and after this period of strain, with inadequate food and drink, we were able to climb down a perilous route under extremely severe conditions. This was the most strenuous of my four ventures in the high Himalayas, but it demonstrated most vividly the marvelous adaptive power of the human body and climaxed my many years of interest in high-altitude physiology.—Some Observations on Acclimatization to High Altitude, Charles S. Houston, M.D., *New England Journal of Medicine*, Dec. 1, 1955.

COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following article has been prepared at the request of the Council on Foods and Nutrition.

EUGENE H. STEVENSON, M.S.
Acting Secretary.

FOLIC ACID AND VITAMIN B_{12} IN MEDICAL PRACTICE

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and
Grace A. Goldsmith, M.D., New Orleans

The practicing physician today is confronted by a seemingly endless array of pharmaceutical preparations that contain varying amounts of folic acid, vitamin B_{12}, or both, with or without the addition of other vitamins, minerals, liver concentrates, or sources of "intrinsic factor." The improper use of preparations containing folic acid and/or vitamin B_{12} may prove futile at best, and at the worst, dangerous to the patient. It is desirable, therefore, to review briefly the nature and metabolic functions of these two vitamins and the indications for their use in medical practice.

Folic Acid

Folic acid (pteroylglutamic acid; folacin) is an essential nutrient belonging to the vitamin B complex. Its distribution in foods is not completely known, largely because it occurs in nature in conjugated forms that have been difficult to measure with accuracy. The extent to which these conjugated forms are broken down and absorbed from dietary sources remains mostly undetermined, but it is known that fresh green, leafy vegetables and organ meats appear to be better sources of folic acid than are lean meats and cereals. In its pure form, folic acid is readily absorbed after oral administration and is excreted, at least in part, in the urine. A substance having activity like that of folic acid is also found in urine; it has been termed the citrovorum factor or folinic acid. This substance, a formyltetrahydro derivative of folic acid, seems to be an intermediary product of the metabolism of folic acid and appears in the urine in increased amounts when folic acid is administered. It possesses greater activity than folic acid itself in promoting the growth of some micro-organisms and in counteracting the toxic effects of folic acid antagonists such as aminopterin and amethopterin. The therapeutic action of citrovorum factor in human subjects is apparently similar to that of folic acid, although the relative activity of the two substances has not been established with certainty.

Methods of microbiological assay for both folic acid and citrovorum factor have been applied to the determination of the concentration of these substances in biological materials such as blood and urine. Such determinations have been of limited value in the detection of folic acid deficiency states in human subjects. The daily requirement of folic acid in man has not been determined, but it appears to be considerably less than 1 mg. Deficiency of folic acid has not been produced experimentally in human subjects; however, the toxic manifestations that follow the administration of folic acid antagonists to man, such as glossitis, gastrointestinal lesions, diarrhea, and anemia, closely resemble the clinical findings in certain naturally occurring diseases that respond to folic acid therapy.

The precise metabolic action of folic acid is not known, but this vitamin appears to play an important role in the synthesis of some of the purine and pyrimidine compounds that are utilized in the formation of nucleoproteins. It is essential for the maintenance of normal hematopoiesis. In animals, it is required for normal growth and for maintenance of gestation. Similar functions of folic acid in man have not been established, although therapeutic abortion has followed the administration of folic acid antagonists to women in the first trimester of pregnancy.

Metabolic interrelationships among folic acid, ascorbic acid, and vitamin B_{12} have been demonstrated but are poorly understood. Much of our information regarding these highly complex interactions is based upon studies with micro-organisms and experimental animals; it needs to be corroborated and extended by careful studies in human subjects before its clinical significance can be evaluated. Vitamin B_{12} and folic acid both seem to be essential in the synthesis of nucleoproteins, although apparently at different stages of the process. Ascorbic acid may play a role in the intermediary metabolism of folic acid. Megaloblastic anemia observed in human infants receiving diets low in or devoid of ascorbic acid has been successfully treated with folic acid or citrovorum factor. Large doses of folic acid correct the abnormal excretion of tyrosine metabolites in patients with scurvy, as does ascorbic acid. Two recent reviews discuss in detail the metabolic functions and interrelationships of these vitamins and their role in hematopoiesis.[1]

Well-established therapeutic uses of folic acid at the present time are in the treatment of the sprue syndrome and the macrocytic, megaloblastic anemias other than pernicious anemia. This group includes the megaloblastic anemia of infancy, the megaloblastic anemia of pregnancy and of the puerperium (the so-called pernicious anemia of pregnancy), megaloblastic anemia associated with primary liver disease or with intestinal strictures or anastomoses, and nutritional macrocytic anemia.

Although folic acid will temporarily correct the hematological abnormalities of patients with pernicious anemia, it has no effect upon the development or progression of the neurological complications of this disease. Thus, a patient with pernicious anemia who is treated with folic acid alone or in conjunction with inadequate amounts of vitamin B_{12}, may develop severe subacute combined degeneration of the spinal cord in the presence of a satisfactory blood picture. This seems to be an increasingly common occurrence. It can be traced, in most instances, to the indiscriminate use of multivitamin

From the Tulane University School of Medicine.

preparations that contain folic acid in therapeutic amounts but that rarely contain sufficient vitamin B_{12}, either with or without intrinsic factor concentrates, to insure the prevention of such complications. Because of this, the routine inclusion of folic acid in vitamin formulas designed for maintenance and stress situations seems unwarranted and potentially dangerous. The presence of one U. S. P. oral unit of vitamin B_{12} in the recommended daily dose of the increasing number of antianemia preparations offered for oral administration is no guarantee that this dosage will be completely safe and effective in a patient. If the slightest doubt exists as to the possibility of a patient's having pernicious anemia, rather than one of the other megaloblastic anemias, vitamin B_{12} given parenterally in adequate dosage should be the initial treatment of choice; folic acid should not be administered unless this therapy proves unsatisfactory. The response to treatment should be evaluated by the accepted criteria for increases in reticulocytes and by changes in the erythrocyte count observed over a period of at least two weeks,[2] as well as by changes in the general clinical condition of the patient.

Some patients with the sprue syndrome and with other non-Addisonian megaloblastic anemias appear to respond as well to the administration of vitamin B_{12} as they do to that of folic acid, but this is not the general rule. Since the megaloblastic anemias of infancy and pregnancy rarely respond satisfactorily to vitamin B_{12}, folic acid is the treatment of choice in these conditions. The recommended daily dose of folic acid is 5 mg. for infants and 15 mg. for adults. The oral and the parenteral routes of administration are equally satisfactory. Treatment should be continued until adequate clinical and hematological response has been obtained. Clinical response to folic acid therapy in patients with sprue or nutritional macrocytic anemia is manifested by disappearance of glossitis, return of appetite, a general feeling of well-being, and improvement in intestinal absorption of fats and carbohydrates in patients in whom absorptive defects are found. In some patients with sprue, however, varying degrees of steatorrhea may persist in spite of therapy. The hematological response to folic acid therapy is similar to that observed during therapy with vitamin B_{12} although, in our experience, it may be somewhat slower. It seems desirable, therefore, to evaluate the initial response to treatment with folic acid over a period of at least four weeks before resorting to some other form of therapy.

It is impossible to state how long therapy with folic acid should be continued in a specific case. After all symptoms have disappeared, after the peripheral blood count and bone marrow have returned to normal, and after necessary dietary adjustments have been made, treatment may be stopped, but the patient should be observed at frequent intervals for any evidence of relapse. The megaloblastic anemia of infancy is not likely to recur after the initial course of therapy if an adequate diet is instituted. Since the megaloblastic anemia of pregnancy may recur with a subsequent pregnancy, it should be guarded against by the administration of 5 mg. of folic acid daily throughout the period of gestation. Some patients with the sprue syndrome or nutritional macrocytic anemia apparently respond completely and permanently to their initial course of treatment; others may relapse several months to several years after cessation of therapy, even though they continue to eat an apparently adequate diet. If indications of relapse become apparent, maintenance therapy with 5 mg. of folic acid daily should be started and continued indefinitely.

Vitamin B_{12}

Vitamin B_{12}, originally isolated from liver in 1948, is generally considered to be identical with the extrinsic factor and the erythrocyte maturation factor of Castle [3] as well as with the so-called animal protein factor. Glandular meats and "fish solubles" appear to be excellent sources of the vitamin; milk, eggs, and muscle tissue contain smaller quantities. Proteins of vegetable origin contain little, if any, vitamin B_{12}. Considerable quantities of the vitamin may be synthesized by the bacteria of the lower intestinal tract of man, but this endogenous source of supply is apparently not available to the host. The normal daily requirement of vitamin B_{12} is not known but may be estimated at 1 mcg. or less. The availability to the organism of the vitamin B_{12} present in foods is unknown.

The structure of vitamin B_{12} has been clarified recently by degradation studies and x-ray crystallography.[4] It is an extremely complex molecule that contains cobalt and phosphorus. Several closely related compounds with vitamin B_{12} activity have been isolated and have received the generic name cobalamins. Vitamin B_{12} itself contains the cyan group and has been designated cyanocobalamin. Vitamins B_{12a}, B_{12b}, and B_{12d}, which are identical, contain the hydroxy group and have been termed hydroxocobalamin. Vitamin B_{12c} contains the nitrite group and is called nitritocobalamin. Vitamin B_{12}, which is prepared commercially from filtrates of cultures of Streptomyces griseus or related organisms, may be obtained in the pure crystalline form or as concentrates of the culture filtrates. The less purified concentrates may produce allergic reactions at times, particularly in patients who have previously received antibiotic therapy. No such reactions have been reported after administration of the crystalline vitamin.

Vitamin B_{12} may be determined quantitatively by chemical, microbiological, or isotopic tracer techniques. Chemical procedures are relatively insensitive and are suitable chiefly for assay of this substance in solutions that contain high concentrations, such as the fermentation broths and crude concentrates of the manufacturing process. None of the microbiological methods is sufficiently simple to be adapted to routine clinical use and they vary considerably in sensitivity and specificity. Ochromonas malhamensis Pringsheim, a chrysomonad, appears to be the organism most specific in its requirement of vitamin B_{12}, but it has been used little, if any, in clinical studies. Another of the algae, Euglena gracilis, has been widely employed in such studies, as have various strains of Lactobacillus leichmannii and some mutant forms of Escherichia coli.

Vitamin B_{12}, isotopically labeled with radioactive Co^{60}, has been employed in a variety of test procedures designed to measure absorption, storage, and excretion of the vitamin; it will be discussed in more detail later. As yet, the metabolic functions of vitamin B_{12} have not

been clearly defined. The vitamin is an essential growth factor in animals and is widely used as a supplement in animal feeds. A similar role in human nutrition has not been established; further work is needed to clarify this important subject. The growth-promoting effects of vitamin B_{12} do not appear to be mediated through any primary influence upon protein metabolism but rather through alterations in carbohydrate and fat metabolism. The vitamin is involved, by way of its participation in the metabolism of purines and pyrimidines, in the synthesis of nucleoproteins and thereby in the maintenance of normal hematopoiesis. Recent investigation suggests that vitamin B_{12} may have a role in the metabolism of methyl, hydroxymethyl, and sulfhydryl groups. It seems certain that vitamin B_{12} is of importance in the metabolism of nervous tissue, although the mechanism of its action is not known.

The tissues of normal persons contain vitamin B_{12} in varying amounts, with the highest concentrations found in the liver and kidneys. Girdwood [5] was unable to demonstrate the presence of the vitamin in the tissues of a patient who died with untreated pernicious anemia. Normal human serum contains vitamin B_{12} in concentrations of 100 to 900 micromicrograms per milliliter, only a small part of which is present as the free vitamin. The majority of the vitamin B_{12} in serum is apparently bound to the alpha or beta globulin fraction of the serum proteins. Patients with pernicious anemia in relapse, as well as some patients with megaloblastic anemias of other origin, have serum concentrations of the vitamin that are definitely below the normal range; in some instances, the presence of vitamin B_{12} cannot be demonstrated. After treatment with vitamin B_{12} or liver extract, serum concentrations return to normal or above, and such levels can be maintained by adequate therapy. Upon cessation of therapy, the serum concentration of Vitamin B_{12} declines as relapse occurs. The bone marrow remains normoblastic as long as serum levels are in excess of 100 micromicrograms per milliliter, becoming megaloblastic at concentrations below this value.[6]

When vitamin B_{12} is given intramuscularly to normal persons or to patients with pernicious anemia in relapse, serum concentrations rise rapidly. Levels reach a maximum within one hour and decline gradually over a period of 24 hours or more. An increase in the amount of vitamin B_{12} in the serum can be detected after the injection of as little as 10 mcg. The vitamin is rapidly excreted in the urine, most excretion occurring within eight hours after administration. The proportion of the dose that is excreted increases with the amount injected; 10 to 25% is found in the urine after the administration of 50 mcg., and 70% or more after the injection of 1 mg.[7] The proportion of a given dose that is excreted in the urine in patients with untreated pernicious anemia does not differ significantly from that excreted by normal persons. This observation suggests that the measurement of urinary excretion of vitamin B_{12} after a single injection of the vitamin does not furnish a reliable index of the state of vitamin B_{12} nutrition. With repeated daily injections of vitamin B_{12}, the proportion of the dose excreted in the urine gradually increases. This is perhaps a reflection of the saturation of body stores.

When vitamin B_{12} is administered orally in a single dose, little or no change in serum levels can be demonstrated, nor is satisfactory hematopoietic response usually observed in patients with pernicious anemia, unless the amount given is 0.5 mg. or more.[8] This quantity is greatly in excess of that which might be obtained from dietary sources. After doses of 3 mg. or more given orally, serum concentrations are definitely increased in both normal persons and patients with pernicious anemia. Maximum serum levels are usually attained within eight hours and are generally comparable to those observed after intramuscular injection of 10 to 50 mcg. In general, increases in serum vitamin B_{12} activity after oral administration of large doses to patients with pernicious anemia are as great as, or greater than, those observed in normal persons, although more variability is evident. The administration of doses of 3 mg. or more to patients with pernicious anemia in relapse is followed by satisfactory hematopoietic response in most instances, and serum vitamin B_{12} levels may remain within normal limits for periods as long as 64 days.[6] Several investigators have demonstrated that it is possible not only to initiate, but also to maintain, remission in patients with pernicious anemia with vitamin B_{12} given orally in large doses.[9] The usual dose required for maintenance has been 1 mg. weekly. Smaller doses have been effective when given daily. Such therapy is not recommended for routine use at the present time, but it offers some advantages in respect to the flexibility of treatment and the standardization of oral dosage, which merit further study.

Most persons who receive 1 to 3 mg. of vitamin B_{12} orally exhibit an increase in urinary excretion of the vitamin. The increase, however, is considerably less than that observed after intramuscular injection of amounts that produce equivalent maximum serum concentrations of vitamin B_{12}. It has been postulated, and substantiated to some extent by recent observations on free and bound forms of vitamin B_{12} in serum, that this difference in urinary excretion may be due to greater binding of the vitamin by serum protein after oral than after intramuscular administration. The free form of the vitamin is apparently readily excreted by the kidney; no significant amount of combined vitamin B_{12} appears in the urine.

Absorption that follows these unphysiological doses of vitamin B_{12} given orally would appear to be caused by some mechanism other than that which is operative in absorption from dietary sources. Effective absorption has been demonstrated after inhalation of aerosols containing vitamin B_{12}, application of the vitamin to the nasal mucosa, and instillation into the rectum.

Microbiological assay techniques have not been satisfactory for study of the absorption and metabolism of physiological amounts of vitamin B_{12} because of the extremely minute quantities involved; however, the production of vitamin B_{12} labeled with radioactive Co^{60} has made possible the application of radioisotope tracer techniques to investigation of this problem. After oral administration of 0.5 mcg. of radioactive vitamin B_{12}, the radioactivity of the feces of normal persons is less than that of patients with pernicious anemia, whether they are in relapse or in remission.[10] When the same dose of radioactive vitamin is administered simultaneously with a source of intrinsic factor, fecal radioactivity of patients

with pernicious anemia decreases to levels comparable to those observed in normal persons, indicating that the intrinsic factor has effected increased absorption or increased retention of the vitamin by the tissues or both. These observations are in accord with the hematopoietic effect of small doses of vitamin B_{12}, administered orally every day in combination with intrinsic factor, in patients with pernicious anemia in relapse.

Observations of comparable significance have been obtained with the "in vivo carrier" technique of Schilling [11] in which the radioactivity of urine is measured after oral administration of radioactive vitamin B_{12}. The vitamin B_{12} is then flushed from the body by a subsequent large intramuscular dose of nonradioactive carrier vitamin. Under the conditions of this procedure, all of the radioactivity that appears in the urine must be derived from the vitamin B_{12} absorbed from the gastrointestinal tract. As might be anticipated, normal persons exhibit higher levels of radioactivity in the urine than do patients with pernicious anemia. After administration of intrinsic factor with the labeled vitamin, radioactivity in the urine of patients with pernicious anemia approaches that found in normal persons. There is no clear-cut evidence that the administration of intrinsic factor increases the amount of vitamin B_{12} absorbed by normal persons.

Although both of the techniques described are relatively satisfactory in distinguishing between normal persons and patients with pernicious anemia, they are not satisfactory in differentiating pernicious anemia from the sprue syndrome. In the latter condition, the extensive defect in intestinal absorption results in findings similar to those of pernicious anemia. In sprue, however, absorption is usually not improved by the administration of intrinsic factor.

Since it is known that vitamin B_{12} is found in relatively high concentrations in the normal liver and is apparently stored in that organ, Glass and his associates [12] have studied the problem of absorption and storage of the vitamin by measuring the amount of radioactivity over the liver area after the administration of radioactive vitamin B_{12}. By comparing the level of radioactivity observed after oral administration of the labeled vitamin to that found after intramuscular injection, an estimate of the amount absorbed may be made. In normal persons, there is apparently decreasing efficiency of absorption with increasing size of oral doses; approximately 90% of a dose of 0.5 mcg. is absorbed as compared with 3% of a 50 mcg. dose. Patients with pernicious anemia showed no significant absorption of small doses of vitamin B_{12} by this technique unless a source of intrinsic factor was given simultaneously.

In view of the limited amount of vitamin B_{12} that can be absorbed by normal persons when it is administered orally and in view of the failure of intrinsic factor to increase this amount, Glass [12] has postulated that there is a "mucosal block" to the absorption of vitamin B_{12} similar to that postulated for the absorption of iron. He believes that in addition to intrinsic factor, which is necessary for transfer of the vitamin across the mucosal membrane, there also must be an intramural "intestinal B_{12} acceptor" like apoferritin that is concerned with absorption of the vitamin. According to this concept, the defect in absorption of vitamin B_{12} in patients with pernicious anemia is caused by lack of intrinsic factor, whereas in sprue the absorptive defect may be caused by lack of intestinal B_{12} acceptor. The analogy to the apoferritin-transferrin mechanism is made complete by postulating that the serum protein fraction that binds vitamin B_{12} functions in a manner similar to that of transferrin.

The primary use of vitamin B_{12} at the present time is in the treatment of pernicious anemia. There is no evidence that liver extract offers any significant advantage over vitamin B_{12} in the therapy of this disease.[13] Under the provisions of the 3rd Supplement to the 14th Revision of the United States Pharmacopeia, both crude and purified liver extracts for injection are now labeled to indicate the content of vitamin B_{12} per cubic centimeter of extract, rather than in terms of "U. S. P. Units (Injectable)." Recommendations for dosage of vitamin B_{12} apply to liver extract as well as to vitamin B_{12} itself.

In the initial treatment of pernicious anemia, intramuscular injection of 50 mcg. of vitamin B_{12} three times weekly for a period of two weeks will produce adequate hematopoietic response in almost all patients. It must be remembered, however, that patients with pernicious anemia vary considerably in their response to therapy. Careful evaluation of the therapeutic response should be made during the period of initial treatment, employing the criteria mentioned previously.[2] The dosage of vitamin B_{12} should be increased if indicated. Symptomatic response is usually evident before any change in the reticulocyte or erythrocyte count can be demonstrated. Within two to five days after the start of treatment, improvement in strength, appetite, and general sense of well-being occurs. Glossitis disappears promptly; fever, if present, subsides; and mental symptoms show rapid improvement. Neurological complications, subacute combined degeneration of the spinal cord and peripheral neuritis, respond less rapidly to therapy, even with large doses of vitamin B_{12}. Some abnormalities may persist permanently, particularly if treatment has been delayed. Current data indicate that doses of vitamin B_{12} that are adequate for the production of satisfactory hematopoietic response are also adequate for treatment of the neurological complications of pernicious anemia. There have been no reports of toxic reactions to the intramuscular administration of doses that far exceed those that are useful therapeutically.

The amount of vitamin B_{12} required for maintenance therapy of patients with pernicious anemia is approximately 1 to 2 mcg. daily. The giving of 100 mcg. intramuscularly at monthly intervals has been found satisfactory for most patients. The use of larger doses given at longer intervals does not seem advisable since the amount of vitamin excreted in the urine increases as the dosage is raised.

In the treatment of pernicious anemia, small doses of vitamin B_{12} in combination with some source of intrinsic factor are effective when given orally. The potency of such preparations is indicated in terms of "U. S. P. Units, Oral." The Anti-Anemia Preparations Advisory Board defines a U. S. P. unit as "that amount of an otherwise acceptable product which produces, when administered daily, clinical and hematopoietic responses in Addisonian pernicious anemia that are considered by the Board to be satisfactory." The "usual dose" indicated by the Board

is one U. S. P. unit daily. This amount should not be regarded as an optimal dose that will produce satisfactory results in every patient. Dosage of oral preparations must be evaluated and adjusted in each patient according to his needs, as is done with vitamin B_{12} or liver extract given parenterally.

Vitamin B_{12} is an effective therapeutic agent in some megaloblastic anemias other than pernicious anemia. The megaloblastic anemia that may follow total gastrectomy is similar to pernicious anemia and should be treated in the same manner. The megaloblastic anemia associated with chronic liver disease may respond to treatment with vitamin B_{12} as well as, or better than, to treatment with folic acid. In some patients with the sprue syndrome or nutritional macrocytic anemia, vitamin B_{12} and folic acid are equally effective, although folic acid is usually the treatment of choice. The dosage of vitamin B_{12} in the aforementioned conditions should be that recommended for pernicious anemia.

Occasionally, deficiency of vitamin B_{12} and folic acid may be present simultaneously in one patient. In such patients, administration of both vitamins may lead to more favorable results than would administration of either vitamin alone. It would seem advisable, for reasons previously discussed, to select vitamin B_{12} as the initial therapeutic agent in cases in which the diagnosis is uncertain. In these instances, daily reticulocyte counts and frequent determinations of hemoglobin and erythrocyte levels should be carried out to determine the efficacy of therapy. If the use of vitamin B_{12} should prove ineffective, it should be discontinued and therapy with folic acid substituted. If this, too, should prove unsatisfactory, the two vitamins may be given together.

Dimorphic anemia, in which deficiency of vitamin B_{12} or of folic acid and deficiency of iron coexist, is not common in this country. This type of anemia may be macrocytic and hypochromic when first seen, or it may be macrocytic and normochromic. In either instance, there may be an initial response to administration of vitamin B_{12} or folic acid that is not sustained, after which the peripheral blood picture changes to that of a microcytic, hypochromic anemia. In such patients, the administration of adequate doses of iron, in addition to the original therapy, will correct the defect.

Vitamin B_{12} has been used as a therapeutic agent in a variety of conditions other than the megaloblastic anemias. Its most widespread application has been in the therapy of a variety of neurological disorders including toxic, diabetic, alcoholic, and nutritional neuropathies, trigeminal neuralgia, and miscellaneous primary degenerative diseases of the central nervous system. Vitamin B_{12} has proved effective in relieving the pain of trigeminal neuralgia in a significant proportion of patients. The usual dosage is 1 mg. or more daily, given intramuscularly. In the treatment of the neuropathies, results have been more variable; sufficient data are not available as yet to permit evaluation of this form of therapy. Vitamin B_{12} apparently offers little benefit in the treatment of degenerative diseases of the nervous system other than subacute combined degeneration, but investigation of such use has been limited.

Vitamin B_{12} has been administered as a dietary supplement in amounts ranging from 5 to 30 mcg. per day in an attempt to correct growth failure in children. Although beneficial effects have been reported in several studies, such supplementation must be considered experimental until more definitive information is available.

Vitamin B_{12} has been suggested as a therapeutic agent in a number of unrelated diseases such as herpes zoster, Ménière's syndrome, psoriasis, chronic discoid lupus, osteoarthritis, viral hepatitis, ulcerative colitis, and allergic dermatoses. In none of these conditions has the value of such therapy been established.

Summary

Both folic acid and vitamin B_{12} are useful in the treatment of megaloblastic anemias. Folic acid is the initial treatment of choice in sprue, nutritional macrocytic anemia, and the megaloblastic anemias of infancy and pregnancy. Vitamin B_{12} is indicated for use in all patients with pernicious anemia, and it should be the initial therapeutic agent employed whenever doubt exists about the etiology of megaloblastic anemia. If the possibility of pernicious anemia exists, the use of folic acid should be avoided because of the hazard of subacute combined degeneration of the spinal cord. For this reason, the inclusion of folic acid in multivitamin and "panhematinic" preparations is potentially dangerous.

In the therapeutic use of either of these vitamins, adequate hematological examinations at frequent intervals are essential in order to evaluate properly the efficacy of treatment. The dosage of either vitamin must be adjusted to the requirements of the individual patient.

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OAK RIDGE RADIOIODINE (I^{131}) FOR HYPERTHYROIDISM—TENTH ANNIVERSARY

GUEST EDITORIAL

Sidney C. Werner, M.D.

The United States Atomic Energy Commission first released radioiodine (I^{131}) for general use in July, 1946. This material was made in the atomic pile at Oak Ridge. Investigations with the isotope were then initiated to determine the clinical value of the isotope in the diagnosis and treatment of hyperthyroidism, in addition to the studies in many other fields. Prior to this, radioiodine had been tried in the treatment of hyperthyroidism. Hertz and Roberts [1] and later Chapman and Maloof [2] had available to them I^{130}, the 12-hour half-life isotope of stable iodine, made in the cyclotron. Hamilton and Lawrence [3] employed I^{131}, the 8-day half-life isotope. Except for the few patients treated by Soley with these latter investigators, I^{131} was not used further until the action of the Atomic Energy Commission; and at that time therapeutic interest in I^{130} virtually ceased.

The highly successful initial trials with I^{131} [4] have led to widespread use of the isotope in the treatment of hyperthyroidism. Inevitably, familiarity with the method has led to a decrease in the fear that carcinogenesis may result from such usage. As a consequence, in some clinics there is a tendency to disregard the restrictions to the isotope's use laid down by most earlier investigators. Moreover, the simplicity and high efficacy of internal radiation therapy have also led to some glossing over of the limitations of the method in the enthusiasm over the virtues.

The 10th anniversary of the release of Oak Ridge I^{131} provides an appropriate occasion at which an objective scrutiny and assessment of the experience to date with the treatment of toxic goiter can be made. This experience should include an analysis of the assembled data from careful long-term follow-up observations. Especially is it time that an unbiased comparison be made between the results of I^{131} therapy and results of surgery and chronic administration of antithyroid drugs. The present-day place of I^{131} in the treatment of hyperthyroidism, in short, needs definition.

Perhaps the major problem in defining the role of I^{131} still is whether this agent is a carcinogen.[5] There is an increasing tendency to consider that the later occurrence of cancer can now be considered unlikely. On this basis, younger hyperthyroid patients are treated with I^{131} in some clinics as freely as older ones. The argument is advanced that since, so far, there has been no increase in incidence of radiation-induced carcinoma of the thyroid in man, by extrapolation it can be predicted that this complication is not so apt to appear later. Most estimates agree that radiation-induced cancer, were it to develop, would do so about 20 years after treatment with I^{131}. Few estimates of time of earliest onset have been expressed. A bell-shaped curve of distribution of incidence of such cancer might reveal onset between 10 to 30 years after therapy, or equally between 18 and 22 years, and still have as the average 20 years. Thus, the fact that cancer has not appeared after 10 years' use is not entirely reassuring. The significance of the fact that cancer may have been induced by I^{131} in one species of rat [6] and not in others [7] is not yet evident.

Another and somewhat specious argument is advanced to justify the use of I^{131} in the patients in the younger age groups. It is brought out that the pathological diagnosis of thyroid cancer is so often erroneous when the later clinical course is unfolded that it would be difficult to establish whether an increase in incidence were due to "pathologist's cancer" [8] or to true clinical cancer. However, should the increase be due to clinical cancer, the point is made that total thyroidectomy could be performed upon those already treated with I^{131} but without known cancer.

Obviously, the histological forms and the degrees of virulence that radiation-induced thyroid cancer might assume are completely unknown. Thus, there is the possibility that the behavior of the disease might preclude prophylactic total thyroidectomy in many. Also, studies with I^{131} in patients upon whom total thyroidectomy has been performed have repeatedly revealed the persistence

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of thyroid tissue. Such remnants might well give rise to carcinoma after I^{131} therapy despite removal of the lobes of the gland.

Subtotal thyroidectomy for toxic goiter carries no risk of late cancer. The remission rate is high. It hardly seems justifiable then to expose the younger patient to radiation from I^{131}, no matter how slight the likelihood of later trouble. However, when hyperthyroidism has recurred after surgery has already been performed, subsequent operations are considerably less effective and carry a greater risk of injury to recurrent nerves and parathyroids. The theoretical risk of cancer formation from I^{131} then becomes much less important than the immediate practical consideration of higher efficiency and lack of the serious complications of surgery.

Another important factor in assessing the place of I^{131} in the therapy of toxic goiter is the increasing frequency with which patients are exposed to radiation from various sources, increased use of x-rays in diagnostic procedures, tests with various isotopes, and occupational exposures being among the many. The question then arises whether a radiation method should be used in treatment if another and almost equally effective method not employing radiation is available.

There are further considerations apart from the radiation aspect. The incidence of hypothyroidism after I^{131} therapy remains high compared to that after surgery. Not only does this complication appear shortly after treatment but its incidence rises progressively during subsequent years.[9] Part of the difficulty can be attributed to the fact that there is no satisfactory method for the calculation of I^{131} dosage. No method currently employed will consistently induce euthyroidism within a given period of time without permitting return of toxicity or development of hypothyroidism in a high percentage of patients. There is a factor of biological variability that makes one patient's gland highly sensitive and another's highly resistant to radiation effect. No method exists for the separation of these extremes from the average. Possibly, an analysis of long-term experience with different dosage methods may reveal an advantage of one over another.

The use of I^{131} has not prevented onset or progression of the complication of severe infiltrative ophthalmopathy. These serious eye changes are likely to progress after subtotal thyroidectomy. However, accurate data concerning their behavior after I^{131} therapy are wanting. Reliable statistics are badly needed, since it must be determined whether Means'[10] early suggestion that I^{131} might have an edge over surgery is valid. It is interesting in this regard that the occurrence and progression of localized myxedema also are seen after I^{131} therapy.[9] Again it is important that the relative incidences following surgery and I^{131} be established.

The negative features of I^{131} therapy in hyperthyroidism should not be taken as minimizing the worth of this method. However, the disadvantages should be as adequately presented as have been the advantages, so that the relative places of I^{131}, operation, and antithyroid drugs in therapy can be defined. The 10th anniversary of the release of I^{131} from Oak Ridge provides the appropriate occasion for the accomplishment of these comparisons.

THE PRICE OF MEDICAL FREEDOM

With the medical profession in many lands practicing under governmental control, it behooves us to inquire into the causes of dissatisfaction of the nonmedical public with the present state of medical care and to convince that public not only that it is receiving better medical care than it ever received before but also that the quality of this care will deteriorate under any system of state medicine. One of the underlying dissatisfactions that exists in spite of spectacular advances in medical knowledge and skill centers around the lack of personal attention given by the modern physician as compared to that given by the old family doctor. Although this is regrettable, it is to a certain extent inevitable. A similar contrast may be seen in the virtual disappearance of the corner grocer, who knew all his customers by their first names and gave an occasional lollipop to a child, and the modern supermarket. Just as the more impersonal supermarket can give better service to a larger number of persons, so can the modern physician or medical team give better medical care than the old family doctor, no matter how sympathetic he may have been. The public is coming to appreciate this, but it cannot be blamed for wishing to hold onto the personal relationship. The physician should never lose sight of the fact that, no matter how scientific his treatment or how full his day, his results can be greatly enhanced by an effort to meet those needs of his patient that are not strictly medical.

Every patient who seeks medical aid is frightened, and one of the most important responsibilities of the physician is to allay the patient's fear. Often without knowing it the hurried impersonal manner of the physician, far from allaying fear, aggravates it. Because patients are becoming better informed medically, much can be done to allay fear by taking time to explain to the patient the nature of his illness, the reasons for the diagnostic and therapeutic procedures recommended, and the results obtained or expected. In a short but discerning article on this problem, Shepard [1] calls attention to the fact that every physician is essentially a teacher and that one of the most important attributes of a teacher is to be able to gauge the patient's ability to understand and apply what he is told. It is equally important to use a positive rather than negative approach. Medical freedom is worth preserving, but it can only be preserved at the price of satisfying the reasonable demands of the "consumer" and creating in his mind an appreciation of the fact that preservation of the system of free enterprise under which modern medical care has reached its present position is his best insurance of continuing advancement in medical knowledge and service.

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ORGANIZATION SECTION

TELEVISION AIDS AVAILABLE TO MEDICAL SOCIETIES

Medical societies desiring to use various anatomic charts and three-dimensional models in presenting their television programs may obtain the loan of a variety of these aids by writing to the Bureau of Health Education at the headquarters of the American Medical Association. These charts and models are available on a loan basis, without charge, except for return postage. Requests should be received by the Bureau of Health Education usually 10 days in advance of the scheduled telecasts. Loaned materials should be returned to the A. M. A. by express not later than 24 hours following telecast. The models will be shipped in special boxes, which the borrower is requested to preserve and return.

The Bureau of Health Education has issued a pamphlet illustrating these charts and models and also listing a series of electrical transcriptions, television-tested scripts with film, filmed programs, and production packets with full instructions to enable any local medical society, with community cooperation and the help of the television staff, to produce a 15-minute television program. This pamphlet also lists 13 15-minute rural health scripts with directions for production over local television stations with rural audiences. All of these various television aids are available to medical societies without charge.

FEDERAL MEDICAL LEGISLATION

Second Session, 84th Congress

Public Assistance Amendments

Representatives Murray (D., Ill.), in H. R. 11038, and King (D., Calif.), in H. R. 10736, would increase the federal contribution in all public assistance programs. In the programs to aid the permanently and totally disabled and the blind, it would be increased to five-sixths of the first $30 paid the recipients each month, and one-half of the balance up to a maximum of $65. In determining the need of recipients the state would disregard: (1) the first $50 per month of earned income; (2) the ownership of a home assessed for less than $5,000; (3) the financial status of relatives; (4) donations of surplus food; and (5) the first $1,200 property value. Congressman Willis (D., La.), in H. R. 11088, would increase similarly the federal contribution for old-age assistance, aid to the blind, and aid to the permanently and totally disabled. All the above bills were referred to the Ways and Means Committee.

Transfer of Veterans' Administration Hospitals

Senator Allott (R., Colo.), in S. 3819, has introduced a measure similar to H. R. 9729, H. R. 9814, and H. R. 9923, previously reported. These measures would prohibit the transfer of Veterans' Administration hospitals to other government agencies without transmitting such proposals to Congress with reasons therefor. Transfer could not be made before the expiration of 90 days of continuous session of Congress following the transmittal date. Either of the two Houses of Congress could block such a transfer. This bill was referred to the Committee on Veterans' Affairs.

Federal Aid to Postgraduate Schools and Scholarships

Congressman Thompson (D., N. J.), in H. R. 11096, would provide a five-year program of grants for maintenance, construction, and scholarships to schools of public health. The program would be administered by the surgeon general of the Public Health Service, assisted by a National Advisory Health Council. Maintenance grants to schools could equal 15% of the basic operating cost of graduate instruction, plus $500 for each full-time student enrolled in excess of 30 such students and an additional sum of $500 for each full-time student enrolled in excess of the school's average past enrollment of such students. The maximum payment to any school, however, could not exceed 50% of its basic operating cost. This measure is similar to H. R. 8859 and S. 1859, previously reported. This bill was referred to the Interstate and Foreign Commerce Committee.

Narcotics Control

Congressmen Boggs (D., La.), in H. R. 11106, Byrnes (R., Wis.), in H. R. 11107, Baker (R., Tenn.), in H. R. 11155, and Sadlak (R., Conn.), in H. R. 11259, would raise the present mandatory sentence of 2 to 5 years to 5 to 20 years for the first offense in trafficking and smuggling narcotics or marijuana. For the second and subsequent offenses, the present 5 to 20 years and a $2,000 fine would be raised to 10 to 40 years and a fine of not more than $20,000. Traffickers who give or sell narcotic drugs or marijuana to a minor would be given a minimum sentence of not less than 10 years and a maximum of up to 40 years, plus a fine of not more than $20,000. For illegal possession of narcotic drugs or marijuana, the sentence would be increased from the present 2 to 5 years for the first offense to not more than 10 years. For second offenders, the present 5 to 10 year sentence would be increased to not more than 20 years, and for third offenders, the present 10 to 20 year sentence and $2,000 fine would be increased to not more than 40 years, plus a fine of $20,000. Authority is given for agents to carry firearms and, under certain circumstances, to use testimony obtained by wire-tapping. All measures were referred to the Ways and Means Committee.

Barbiturate and Amphetamine Drugs Control

Congressmen Boggs (D., La.) and Byrnes (R., Wis.), in H. R. 11108 and H. R. 11109, respectively, propose to require registration of manufacturers, compounders, and processors of barbiturate and amphetamine drugs.

Prepared by the Washington Office of the American Medical Association.

Manufacturers, compounders, processors, and handlers would be required to maintain a complete record of all barbiturates and amphetamines on hand and sold and to preserve such record for a period of three years. Medical practitioners licensed by law to prescribe or administer barbiturates or amphetamines, who dispense such drugs in the course of their professional practice, are excused from record-keeping. Both measures were referred to the Interstate and Foreign Commerce Committee.

National Library of Medicine

Congressmen O'Brien (D.), in H. R. 11267, Bowler (D.), in H. R. 11268, Boyle (D.), in H. R. 11269, Kluczynski (D.), in H. R. 11270, Murray (D.), in H. R. 11271, O'Hara (D.), in H. R. 11272, Sheehan (R.), in H. R. 11273, and Yates (D.), in H. R. 11274, all of Illinois, would create a National Medical Library to which the Armed Forces Medical Library books and periodicals would be transferred. It is similar to S. 3430, previously reported, except it would locate the library in the city of Chicago. All measures were referred to the House Administration Committee.

Codification of Veterans Compensation Laws

Congressmen Teague (D., Texas) and Saylor (R., Pa.), in H. R. 10046 and H. R. 10439, respectively, propose to simplify and codify the present law that relates to compensation and presumption of service-connection for diseases and disabilities. It does not increase or decrease the veterans compensation. A presumption of service-connection is continued in cases of chronic or tropical diseases becoming manifest within one year after separation from active service, active tuberculosis becoming manifest within three years, and multiple sclerosis becoming manifest within two years. This bill was written by the committee staff and agreed to by the Veterans Administration and the Bureau of the Budget. After extended hearings, this was reported favorably by the Veterans' Affairs Committee to the House, was promptly passed, and was sent to the Senate. Both measures were reported to the Veterans' Affairs Committee.

Medical Care for Persons Aboard U. S. Vessels

Delegate Bartlett (D., Alaska), in H. R. 10069, and Senator Magnuson (D., Wash.), in S. 3677, would amend the Public Health Service Act that currently provides that seamen employed on vessels of United States registry are entitled to medical, surgical, and dental treatment and hospitalization without charge at Public Health Service hospitals. The proposed amendment would extend the eligibility to "any person employed or engaged on board." This would extend such care to the masters and owners of the vessels. This was referred to the Interstate and Foreign Commerce Committee of both Houses.

Medical Expenses for Retired Railroad Employees

Congressman Ashley (D., Ohio), in H. R. 9740, proposes to amend the Railroad Retirement Act to provide for the payment of personal medical expenses of pensioners from the Railroad Retirement Fund. Payments could not exceed $400 in any one calendar year and would be in addition to the annuity or pension provided by the act. This measure was referred to the Interstate and Foreign Commerce Committee.

Social Security Amendments

Retirement Age and Disability Benefits.—Congressman Bennett (R., Mich.), in H. R. 9741, proposes to liberalize the Social Security Act to include (1) disability insurance benefits for disabled individuals who have attained the age of 50, (2) reduction of the pension age for men from 65 to 62, and to age 60 for women (widows would become eligible at age 55), and (3) increase of pension benefits from 33.3% per month in the lowest bracket, to be scaled downward to 10% in the highest bracket. Congressman Flood (D., Pa.) has introduced, in H. R. 10064, a proposed amendment to the Social Security Act that would reduce the retirement age to which OASI benefit payments would begin from 65 to 60 in the case of men, and 55 in the case of women. Retirement benefits would begin at once for fully insured individuals who become permanently and totally disabled.

Old-Age Assistance.—Congressmen Albert (D., Okla.), in H. R. 9900, Boggs (D., La.), in H. R. 10026 and H. R. 10457, Willis (D., La.), in H. R. 10186, and Thompson (D., La.), in H. R. 10275, have introduced similar measures that would increase the present federal contribution to states for old-age assistance from four-fifths of the first $25, to five-sixths of the first $30, multiplied by the total number of individuals in a state receiving old-age assistance for each month. The federal share of all amounts over the first $30 up to $65, paid to any individual for any month, would be on a matching basis with state contributions. The maximum limit to which the federal government now participates is $55 per month. H. R. 10026, H. R. 10186, and H. R. 10275 would require that the state maintain their expenditures for such assistance at or above the 1955 level. H. R. 10457 would increase the federal contribution similarly for aid to the blind and aid to the permanently and totally disabled. Congressman Moulder (D., Mo.), in H. R. 10076, would increase federal payments to five-sixths of the first $35 and provide for matching contributions up to $75 per month per recipient. Congressman Dingell (D., Mich.), in H. R. 10104, proposes, among other amendments, similar increases to those in H. R. 9900, above, for old-age assistance and aid to the needy and permanently and totally disabled.

Hospitalization for the Aged and Dependents and Survivors.—Congressmen Dingell (D., Mich.) and Metcalf (D., Mont.), in H. R. 9868 and H. R. 9980, respectively, would amend the Social Security Act to provide hospitalization for "insured" aged persons and their dependents and for the survivors of deceased "insured" persons. Payments would be made from the OASI Trust Fund for up to 60 days' hospital expense annually. Excluded from coverage would be charges for surgery or medical care, except such charges as are generally provided by hospitals. These measures were referred to the Ways and Means Committee.

Water Pollution Control Act Extension and Amendment

Congressman Blatnik (D., Minn.), in H.R.9540, would extend and strengthen the Water Pollution Control Act that is due to expire shortly. There would be provided matching grants of 2 million dollars to states and interstate agencies for each of the next five years for general water pollution control work. Construction grants for sewage treatment works for states, municipalities, and intercity or interstate agencies on a 50-50 matching basis would also be authorized. Eligible treatment works would be those servicing communities of 125,000 population or under. The bill strengthens the enforcement procedures by (*a*) providing for a conference of federal officials and state agencies before an action is taken, (*b*) providing for a finding of interstate pollution to be made subsequent to the holding of a special hearing by a representative board (under the present law the surgeon general can make a finding of interstate pollution prior to a public hearing), and (*c*) providing for federal court action to be taken on the request of a state that is polluted by an upstream offender as well as with the consent of the state where the pollution originates. The present advisory board, made up of federal and nonfederal members, would be replaced by a board having a federal chairman and nine nonfederal members. The bill would make the water pollution control program permanent. This bill was referred to the Committee on Public Works.

COUNCIL ON MENTAL HEALTH

COMMITTEE ON ALCOHOLISM

Marvin A. Block, M.D.

The Committee on Alcoholism of the American Medical Association, a committee of the Council on Mental Health, wishes to announce to the profession that it has completed arrangements for a new service to physicians. In 1955, the Committee acquired a copy of the Classified Abstract Archive of the Alcohol Literature. This collection of abstracts was developed by Jellinek, Keller, and Efron at the Yale Center of Alcohol Studies. It contains in condensed form the outstanding scientific literature on alcohol and alcoholism from all over the world. The purpose of the archives is to give easy access to any selected topic in the vast accumulation of the published materials on alcohol problems. Abstracts of relevant literature are classified by subject matter. The abstracts are printed on "finding" cards, and the subject content is indexed in code along the margins. By inserting a sorting needle through prepared holes in the margins of these cards, it is possible to assemble literature on any specific topic according to the appropriate subject code. In a comparatively short time a bibliography or abstracts of the literature on a desired phase of alcohol can be obtained.

The Committee on Alcoholism has made arrangements whereby topical bibliographies and photocopies of selected abstracts can be made available to physicians at a very nominal cost. Bibliographies and abstracts that may be ordered by number from such bibliographies will be mailed to any physician upon request and on payment of a small fee to cover the cost of handling.

Since there are many thousands of abstracts on an infinite number of phases of alcohol and alcoholism, it is essential that the subject matter requested be defined as precisely as possible. Generalizations would result in obtaining such large numbers of references as to be of little practical use. Each request should be focused as nearly as possible upon one phase of the problem. As many particular definite phases as one desires may be requested, but generalizations should be avoided. The main topics treated, each of which has been subdivided into 50 to 80 further subject headings, are as follows:

A: Metabolism of Alcohol
B: Biochemistry, Experimental
C: Biochemistry, Clinical
D: Physiology, Experimental
E: Physiology, Clinical
F: Nutrition
G: Medical Complications of Alcoholism, Experimental
H: Medical Complications of Alcoholism, Clinical
I: Mental Disorders
J: Psychology, Experimental
K: Psychology, Clinical
L: Alcohol Addiction or Alcoholism
M: Treatment of Alcoholism; Rehabilitation of Inebriates
N: Treatment of Medical Complications of Alcoholism and Alcohol Intoxication
O: Heredity and Germ Damage
P: Sociology, Anthropology, Culture, Customs, History
Q: Geographical-Ethnological Divisions
R: Statistics, Medical
S: Statistics, Socioeconomic
T: Legal Aspects
U: Alcohol Determination, Methodology
V: Alcoholic Beverages and Alcohols
W: Education and Propaganda

An example of how the main subject is subdivided is illustrated for heading L.

L: Alcohol Addiction or Alcoholism
1, women; 2, children, adolescents; 3, alcoholism; 4, alcohol addiction; 5, symptomatic drinking; 8, nonaddictive excessive drinking; 10, ex-alcoholics; 11, classification, definition; 15, therapy; 16, diagnosis; 17, typology; 18, drinking pattern; 19, kind of beverage; 20, etiology; 26, constitution; 29, allergy, susceptibility, idiosyncrasy to alcohol; 31, predisposition; 32, diet, nutrition; 33, prevention; 35, psychoanalysis; 36, hypnosis, narcoanalysis; 42, heredity; 48, sex, except homosexuality; 49, homosexuality; 50, abstinence versus moderation in ex-alcoholics; 69, suicide; 75, family constellation; 77, spouse, marital status.

Bibliographies on definite parts of any of the main topics (indicated by the code letters) should be requested in as completely defined terms as possible, limiting each separate request to one particular phase of the main topic. This will help avoid extensive numbers of selections not pertinent to the required information.

Since there are only nine sets of these abstracts in the United States, the Committee feels that this service should be of value to all physicians interested in the problems of alcoholism, and especially to those with a research interest. For further information and requests for bibliographies and abstracts, please address the Committee on Alcoholism of the American Medical Association at its headquarters, 535 N. Dearborn St., Chicago 10.

Chairman, Committee on Alcoholism.

MEDICAL NEWS

CALIFORNIA

Symposium for Laboratory Technicians.—The fifth annual Symposium for Laboratory Technicians will be at the University of California at Los Angeles June 23-24. The symposium will include: Tuberculosis Bacteriology—Chemotherapy; Instrumentation; and The Pancreas. Programs may be obtained on request to University of California at Los Angeles Extension (BRadshaw 2-6161).

Institute on Industrial Health.—Sponsored by the state department of public health, an institute on industrial health practices will be held June 21-22 in Earl Warren Hall, University of California School of Public Health in Berkeley, for public health personnel in northern California. One session of the institute will be devoted to environmental factors affecting occupation health problems and practices and one will explore the human factors.

CONNECTICUT

Dr. Cooke Goes to Johns Hopkins.—Dr. Robert E. Cooke, associate professor of pediatrics, Yale University School of Medicine, New Haven, has been appointed professor and head of the department of pediatrics in the Johns Hopkins University School of Medicine, Baltimore, and pediatrician-in-chief of the Johns Hopkins Hospital. He will complete the current academic year at Yale and assume his new position at the end of June. Dr. Cooke will succeed the late Dr. Francis F. Schwentker.

The Barker-Weld Conference Room.—The Connecticut State Medical Society announces that a new conference room being constructed as an addition to its office building in New Haven will be named in honor of Dr. Creighton Barker, New Haven, executive secretary of the society, and Dr. Stanley B. Weld, Hartford, managing editor of the *Connecticut State Medical Journal*. The tribute marks the 20th anniversary of the founding of the journal and establishment of a full-time administrative headquarters for the state medical society. Drs. Barker and Weld were honored also at the recent annual dinner of the society, when they were presented with inscribed silver trays in recognition of their long periods of service. Dr. Barker's service as executive secretary of the society began in 1936, the year in which the journal was founded and Dr. Weld was elected managing editor.

ILLINOIS

Clinics for Crippled Children.—The University of Illinois division of services for crippled children has scheduled the following clinics to which any private physician may refer or bring children for consultative services:

June 26, Effingham (rheumatic fever), St. Anthony's Emergency Hospital; Peoria, Children's Hospital.

June 27, Elgin, Sherman Hospital; Springfield (cerebral palsy), Memorial Hospital.

June 28, Bloomington, a.m. (general), p.m. (cerebral palsy), St. Joseph's Hospital.

Chicago

Symposium on Oral Cancer.—An all-day oral cancer symposium will be presented June 20 at Thorne Hall, Northwestern University (Superior Street and Lake Shore Drive), under the sponsorship of the American Cancer Society, Illinois Division, in cooperation with Northwestern University Dental School; Loyola University, Chicago College of Dental Surgery; University of Illinois College of Dentistry; and the Chicago and Illinois State Dental societies.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

MARYLAND

New Alpha Epsilon Delta Chapter.—Alpha Epsilon Delta, the national premedical honor society, announces the installation of the Maryland Alpha chapter at the Johns Hopkins University, Baltimore, Feb. 11. Charter members of the chapter included 29 students and 4 members of the faculty. Dr. Samuel P. Asper, associate professor of medicine at Johns Hopkins University, was the guest speaker at the installation banquet.

Dr. Ravitch Returns to Baltimore.—Dr. Mark M. Ravitch, for more than 20 years student, resident, and faculty member in the department of surgery at Johns Hopkins University School of Medicine, recently returned to Baltimore as surgeon-in-chief at Baltimore City Hospitals after three years as clinical professor of surgery at Columbia University College of Physicians and Surgeons and head of the department of surgery at Mount Sinai Hospital, New York City. On his return he was reappointed associate professor of surgery in the Hopkins school of medicine and surgeon on the hospital staff. Dr. Ravitch, who served in the European Theatre as assistant chief of surgery and chief of thoracic surgery with the 56th Army General Hospital, from 1943 to 1946, went to England in 1949 as exchange professor in surgery to Guy's Hospital in London and was subsequently appointed honorary associate consulting surgeon.

MINNESOTA

Camp for Physically Handicapped.—Camp Courage, Minnesota's only camp especially designed for physically handicapped children and adults, will open its second season June 17. The camp, maintained by the Minnesota Society for Crippled Children and Adults (Easter Seal Society, 1639 Hennepin Ave., Minneapolis 3), is located on Cedar Lake, about four miles northwest of Minneapolis. It offers regular activities as well as speech and physical therapy on recommendation from a physician. An occupational therapist administers the arts and crafts program. The camp is open to all types of physically handicapped children (minimum age, 8) and adults. The camp is not accepting mentally retarded or emotionally disturbed children. Epileptics, diabetics, and enuretics are screened by an admission committee on medical recommendation. No applicant is refused admission because of race, creed, color, or inability to pay.

MISSOURI

Society News.—On June 22 Dr. Harold D. Kautz, Chicago, Secretary, Council on Pharmacy and Chemistry, American Medical Association, will address the Greene County Medical Society on "The Problems of Pharmacy and Medicine." Pharmacists and pharmaceutical representatives will be guests of the society.

Special Education Conference.—A special education conference will be held, June 21-22, as a part of the 1956 University of Missouri summer session. Speakers will include Bob Gates, director of special education in the state of Florida; Samuel A. Kirk, Ph.D., director of the Institute of Research for Exceptional Children at the University of Illinois, Urbana; and Ray Graham, M.S., director of special education for the state of Illinois.

MONTANA

Personal.—Dr. Lester S. McLean, formerly director of local health services, Montana Board of Health, Helena, was recently made Humboldt county health officer in Eureka, Calif.—— Dr. Howard W. Bateman, Choteau, retired recently after 48 years in the practice of medicine. Dr. Bateman has served as mayor of Choteau, as state senator, and as a member of the state board of medical examiners. He is a veteran of the Spanish-American War and World War I. Dr. Bateman was recently honored at a banquet given by Lions District 37C, which embraces parts of Montana and Alberta, Canada, and which he serves as governor.

General Practice Meeting in Livingston.—The Montana Academy of General Practice will hold its sixth annual scientific assembly June 22-23 at the Elks Club, Livingston, under the presidency of Dr. Joseph S. Pennepacker, Sidney. His address of welcome at 8:45 a. m. will be followed by "Clinical Use of Ataraxics" by Dr. H. Ryle Lewis, Missoula, after which a film, "Pharmacodynamics of Ataraxics," will be presented by Dr. Joseph F. Fazekas, Washington, D. C., through the courtesy of Wyeth Laboratories. Questions and a panel discussion, preceded by "Some Common Dermatoses" by Dr. C. Gordon Vaughn, Minneapolis, will conclude the morning session. The afternoon session will open with "Use of Corticotropin and the Adrenocorticoid Steroid Hormones in Treatment of Renal and Cardiac Diseases" by Dr. John A. Layne, Great Falls. "Diseases of Adrenal Cortex" will be presented by Dr. Perry S. MacNeal, Philadelphia, and "Management of Intestinal Obstruction" by Dr. Manuel S. Lichtenstein, Chicago, before the concluding afternoon questions and panel discussion. A cocktail hour and trout fry at Stump Island, 6:30-9:30 p. m., will precede an informal dance at the country club. After a welcoming address by the mayor of Livingston, Saturday, 9:45 a. m., "Trends in Hospital and Health Care" will be considered by Mr. T. O. Peterson, St. Paul. The Saturday morning program will include "Some Aspects of Colon Surgery" by Dr. Arthur W. Ide Jr., Minneapolis; "Office Management of Diabetes Mellitus" by Dr. MacNeal; and "Preoperative Care and Postoperative Management of Surgical Patients" by Dr. Lichtenstein. At the noon banquet, 1 p. m., the guest speaker, Dr. Josiah J. Moore, Chicago, Treasurer, American Medical Association, will discuss "Responsibilities of the General Practitioner."

NEW HAMPSHIRE

Personal.—Dr. Charles S. Houston, Exeter, was guest speaker at the 109th annual meeting of the Providence Medical Association at the Rhode Island Medical Society Library, Jan. 9. His subject was "Personal Observations Made at Very High Altitudes." Dr. Houston organized the British-American party that climbed Nanda Devi, 25,600-ft. peak in the central Himalayas, and in 1950 he and his father made the first approach to Mt. Everest from the south, being the first white men to cross this section of Nepal.

Meetings on Alcoholism.—The second annual North Conway Institute on Alcoholism, a closed meeting for the clergy and interested laymen, will be sponsored, June 18-22, by the North Conway Foundation, North Conway.—"Alcoholism," an address by Father Thomas Foley, Medford, Mass., before the Laconia Committee on Alcoholism, June 20, will be open to the public. ——Tentative dates (June 25-July 13) have been scheduled for a course on "Alcohol Education" for school teachers in Concord, which will be sponsored by Keene Teachers College and the state department of health, division on alcoholism.

NEW YORK

Speakers on Diabetes Mellitus.—The Clinical Society of the New York Diabetes Association has a panel of speakers who will be available on request of hospital groups in the metropolitan area for discussion of various aspects of diabetes mellitus. Requests should be sent to the Clinical Society of the New York Diabetes Association, 270 Park Ave., New York 17.

Community Nutrition Institute.—The 10th annual Community Nutrition Institute, sponsored by the college of home economics of Syracuse University and the bureau of nutrition of the state health department, will be held at the university June 18-30. Topics for discussion will include presentations on growth, heredity, anthropology, and the medical, psychological, nutritional, and social needs of pregnancy, infancy, childhood, and adolescence.

New York City

Plastic Surgery Clinic Dedicated.—A clinic for reconstructive plastic surgery of the face was recently dedicated at the Manhattan Eye, Ear, and Throat Hospital, 210 E. 64th St. The $100,000 12-room clinic, which occupies the second floor of the hospital's east wing, is a gift of the Society for the Rehabilitation of the Facially Disfigured, Inc. Speakers at the dedication included Drs. Howard A. Rusk, director of physical medicine and rehabilitation, New York University-Bellevue Medical Center; Basil C. MacLean, commissioner of the department of hospitals; and R. Townley Paton, chairman of the board of surgeon directors at the hospital.

OKLAHOMA

State Medical Election.—Newly elected officers of the Oklahoma State Medical Association include Dr. John F. Burton, Oklahoma City, president-elect, and Dr. Forrest S. Etter, Bartlesville, vice-president.

Hospital News.—A recently announced $229,880 expansion program for Children's Medical Center of Tulsa will add 20 beds to the 42 now in use. The program is being financed by $103,333 in federal matching funds made available under the Hill-Burton hospital act and $24,100 contributed to the center recently by the Ford Foundation, with the balance to come from public subscription. The building program will include a new convalescent wing, kitchen, dining room, and reception room, plus widespread remodeling of the old hospital building.

PENNSYLVANIA

Health Education Workshops.—Health education workshops for teachers, nurses, school administrators, dental hygienists, guidance workers, and parents interested in community-school health programs have been scheduled at the following institutions: Pennsylvania State University, University Park, June 11-29; University of Pittsburgh, June 18-29; Lehigh University, Bethlehem, June 19-July 6; State Teachers College at Slippery Rock, June 25-July 13; West Chester State Teachers College, June 25-July 13; and Temple University, Philadelphia, July 2-20. Applicants for scholarships should contact their county superintendent of schools or the executive secretary of their local tuberculosis and health association.

Philadelphia

Hospital News.—President Eisenhower's personal physician, Major Gen. Howard McC. Snyder, recently addressed the Founders' Day luncheon of the Presbyterian Hospital in Philadelphia, where he interned in 1905 and 1906. Other guests were Dr. Albert E. Blackburn, a member of the hospital's medical staff, who was a resident chief at Presbyterian when Major General Snyder interned there; Dr. James R. Martin, associate dean, Jefferson Medical College of Philadelphia, and nine of Major General Snyder's Jefferson classmates.

Dr. Macfarlane Honored.—At a gala 79th birthday dinner tribute on April 7, Dr. Catharine Macfarlane received an illuminated scroll made by the nuns of the Convent of the Good Shepherd in Germantown, bearing the names of alumnae, faculty, friends, staff, and dinner guests, whose collective birthday gift totals over $10,000, which is to be used for the Catharine Macfarlane Cancer Control Center for teaching and research at the Woman's Medical College of Pennsylvania. The center will be part of the new wing to be erected through the college's current 4-million-dollar development program.

ALASKA

Speech and Hearing Program.—A speech and hearing therapy program on a demonstration basis was recently initiated in Juneau, Ketchikan, and Sitka under the sponsorship of the Alaska Department of Health in cooperation with southeastern Alaska chapters of the Alaska Crippled Children's Association.

Personal.—Dr. Fred M. Langsam, medical director of the Maynard MacDougall Memorial Hospital at Nome, has submitted his resignation after seven years' service. The hospital, which is operated by the Methodist Church, was recently granted accreditation by the Joint Commission on Hospital Accreditation. It is said to be the first one-physician hospital ever to be so accredited.——Dr. Richard C. Murphy, health officer for the Greater Anchorage Health district since 1954, has been appointed regional health officer for the southcentral Alaska health region with headquarters in Anchorage, to succeed Dr. Jack B. Eason, who resigned last summer.

GENERAL

Aero Medicine Medal.—Establishment of the Aero Medicine medal, an annual award to be presented for the outstanding contribution to basic research in aviation medicine, was announced April 18 at the 27th annual meeting of the Aero Medical Association in Chicago. The award, consisting of a bronze medal and a $500 honorarium, is sponsored by Pfizer Laboratories, a division of Chas. Pfizer & Company, Inc., Brooklyn, N. Y., pharmaceutical firm. In choosing the recipient of the award, primary consideration will be given to scientific papers published in the association journal, the *Journal of Aviation Medicine*, but such publication will not be required for a scientific contribution judged to be of outstanding merit.

Meeting on Nuclear Medicine.—The Society of Nuclear Medicine will hold its annual meeting at the Hotel Utah, Salt Lake City, June 21-23 under the presidency of Dr. Milo T. Harris, Spokane, Wash. About 50 papers will be presented. The sessions will open with "Studies of Blood Volume in Man: 1. Total Blood, Plasma, and Red Cell Volume in Normal Subjects" by Dr. Robert E. Zipf, Dr. Joe M. Webber, and G. Richard Grove, Ph.D., Dayton, Ohio. The closing presentation will be "Diagnostic Value and Interrelationships Among Thyroid Clearance Uptake and Rate of Uptake in Hyperthyroidism" by Dr. Alvin L. Schultz (by invitation) and Dr. Leslie Zieve, Minneapolis. A visit to the Radiobiology Laboratory, University of Utah College of Medicine, Salt Lake City, has been arranged to follow the program.

Neurologists Meet in Atlantic City.—The 81st annual meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, N. J., June 18-20. The sessions will open with the presidential address by Dr. Johannes M. Nielsen, Los Angeles, which will be followed by "The Prognosis in Hemiballismus" by Drs. Herbert H. Hyland and Dayton M. Forman, Toronto, Canada. The Monday evening session, 8 p. m., will be devoted to motion picture demonstrations. Cocktails, Tuesday, 7 p. m., will precede the annual dinner at 8 p. m. The American Association of Neuropathologists will meet on Saturday and Sunday preceding the meeting of the American Neurological Association and the American Electroencephalographic Society on Friday, Saturday, and Sunday. A symposium on cytopharmacology has been scheduled for Saturday and Sunday. All these sessions will be at the Claridge Hotel.

Annual Meeting on Dermatology.—The American Dermatological Association will hold its 76th annual meeting at the Santa Barbara Biltmore, Santa Barbara, Calif., June 18-21, under the presidency of Dr. Vincente Pardo Castello, Havana, Cuba. The presidents' party for Dr. and Mrs. Pardo Castello and for Dr. C. Ferd Lehmann, San Antonio, Texas, vice-president, and Mrs. Lehmann will be given Monday, 6:30 p. m. The sessions will open at 10:30 a. m. with the presidential address, "Dermatology in a Tropical Rural Zone with a Reference to Occupational Dermatoses." In all, 25 papers have been scheduled, the concluding one being "Cutaneous Responses to the Sting of the Imported Fire-Ant (Solenopsis Saevissima)" by Dr. Marcus R. Caro, Chicago. The association golf tournament for men and women is scheduled for Wednesday afternoon and the awarding of golf trophies for Thursday, 11:30 a. m.

Annual Orthopedic Meeting.—The American Orthopaedic Association will hold its 69th annual session June 20-23 at the Banff Springs Hotel, Banff, Canada. Dr. Paul C. Colonna, Philadelphia, president, will deliver the presidential address Friday at 11:15 a. m. The president's reception is scheduled for 6:30 p. m. Wednesday. The session will open Wednesday at 9 a. m. with "Cervical Spine Fractures and Dislocations Treated with Dependent Head Traction" by Dr. Hira E. Branch, Flint, Mich. (by invitation). Other invited speakers at the Wednesday program will include Dr. Jean Verbrugge, Antwerp, Belgium, who will give "An Evaluation of the Surgical Use of Metals in Children"; Henry A. Lepper Jr., D. Eng., New Haven, Conn., who will participate with Dr. Charles O. Bechtol, New Haven, in presentation of "Biomechanical Problems of Placing Metal Screws in Bone"; and Dr. Robert Merle D'Aubigne, Paris, France, who will participate in discussion of "Further Evaluation of the Use of Intramedullary Nailing in the Treatment of Gunshot Fractures of the Extremities" by Col. Ernest A. Brav, M.D., Washington, D. C. At 11:35 a. m. Thursday "Treatment of Volkmann's Contracture by Excision of the Infarct" will be discussed by Dr. Herbert J. Seddon, clinical director, Royal National Orthopaedic Hospital, and director of studies, Institute of Orthopaedics, London, England. The program lists a dozen other invited speakers. On Tuesday at 9:30 p. m. a hobby-travelogue program, "Points of Interest in the Beautiful Canadian Rockies," will be presented by Dr. M. Beckett Howorth, Stamford, Conn., and another such program will be given Wednesday at the same time and will include "A Motor Trip Through Ireland and Scotland" by Dr. Don H. O'Donoghue, Oklahoma City; "Fascinating Ports of the Mediterranean" by Dr. Robert C. Lonergan, St. Petersburg, Fla.; and "Color, Gold and Water in the Far East" by Dr. James E. M. Thomson, Lincoln, Neb. An informal cocktail party is scheduled for Thursday, 7 p. m., and the annual banquet for Friday, 7 p. m. The golf tournament is scheduled for 2 p. m. Friday.

Annual Meeting of Medical Librarians.—The Medical Library Association will hold its 55th annual meeting at the Hotel Statler, Los Angeles, June 18-22. A program on the Audio Digest has been arranged for Monday, 8 p. m., in the auditorium of the Los Angeles County Medical Association, 1925 Wilshire Blvd. At the general session Tuesday morning Dr. Roger O. Egeberg, medical director, Los Angeles County (General) Hospital, will talk on medicine in Los Angeles, and Dr. Charles W. Shilling, deputy director, Division of Biology and Medicine, U. S. Atomic Energy Commission, Washington, D. C., will consider "The Medical Library as a Communications Center." The following program will be presented Tuesday, 8-9:30 p. m., at a medical society group meeting:

Trends in Medical Indexes and Abstracting Tools, Miss Estelle Brodman, reference librarian, Armed Forces Medical Library, moderator.
Current List of Medical Literature, Lieut. Col. Frank B. Rogers, librarian, Armed Forces Medical Library.
Quarterly Cumulative Index Medicus, Miss Magdalene Freyder, librarian, American Medical Association.
Excerpta Medica, P. A. Warren, director, Excerpta Medica.
Related Tools and Specialized Medical Indexes, Sanford V. Larkey, librarian, and John M. Whittock Jr., assistant librarian, Welch Medical Library, Johns Hopkins University, Baltimore.

Wednesday has been designated as medical schools day. The sessions will be held at the University of California at Los Angeles at 9:30 a. m. Welcoming addresses will be delivered by Dr. Raymond B. Allen, chancellor, and Lawrence C. Powell, Ph.D., librarian. Before luncheon there will be a panel on the application of atomic energy to biological problems, in which Dr. Thomas G. Hennessy, chief, radiobiology division, Atomic Energy Project, University of California, Los Angeles, will participate. After luncheon Dr. Cyril B. Courville, professor of neurology, College of Medical Evangelists, Los Angeles, will discuss "Brain Injury on the Western Frontier," and Dr. Stafford L. Warren, dean, University of California School of Medicine at Los Angeles, will talk on the medical center at his university. On Thursday at 2 p. m. John Field, Ph.D., professor of physiology, University of California School of Medicine at Los Angeles, will present "Changing Concepts in the Medical Schools and Their Libraries." At the banquet, 7 p. m., the program will be "Medic," with Jerry L. Pettis, public relations counsel, Los Angeles County Medical Association, coordinator; Mr. James Moser, creator and writer; and Mr. Richard Boone, actor. The final session will be held Friday morning, when the following program will be presented:

In Quest of Death Dealing Fishes, Bruce W. Halstead, chairman, department of biotoxicology, School of Tropical and Preventive Medicine, College of Medical Evangelists, Loma Linda, Calif.
Health Crosses the Pacific, Wilton L. Halverson, professor of public health, University of California School of Medicine at Los Angeles.
Medicine Moves West, Donald A. Charnock, Los Angeles, president, California Medical Association.

Joint Meeting of American and Canadian Technologists.—The annual meetings of the American Society of Medical Technologists and the Canadian Society of Laboratory Technologists, which will be held jointly June 17-22 at the Chateau Frontenac, Quebec, Canada, will be the first North American Conference of Medical Laboratory Technologists. The keynote speaker

Monday, Dr. F. Kauffmann, chief, International Salmonella and Escherichiae Center, Statens Seruminstitut, Copenhagen, Denmark, will present "The Principles of Biochemical and Serological Differentiation of Enterobacteriaceae." An afternoon symposium, "The Practical Laboratory Approaches to Enteric Disease with Special Emphasis on Cold Climate Aspects," will be cosponsored by Lederle Laboratories Division, American Cyanamid Company, and North American Cyanamid Limited. Harold J. Fournelle, Ph.D., chief of bacteriology, Arctic Health Research Center, U. S. Public Health Service, Anchorage, Alaska, will discuss his experience with the laboratory diagnosis of enteric disease in Alaska, will show colored lantern slides of equipment he takes to the field and the type of laboratory he sets up in Eskimo villages, and will discuss problems of transportation and the actual work done preliminary to the typing of cultures. Dr. William R. Bailey, bacteriologist, Department of National Health and Welfare, Ottawa, Canada, will discuss the laboratory diagnosis of enteric disease in Canada. Philip R. Edwards, Ph.D., bacteriologist, Communicable Disease Center, U. S. Public Health Service, Chamblee, Ga., will talk on "Practical Considerations in Salmonella and Shigella Typing." Evan T. Bynoe, Ph.D., chief, Bacteriological Laboratories, Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, will summarize the discussion. A biochemistry refresher course will offer a seminar in clinical hemoglobinometry on Monday and one on blood glucose Tuesday. These seminars, conducted by Dr. F. William Sunderman, Philadelphia, and Dr. Bradley E. Copeland, Boston, will include technical motion pictures made at the Naval Medical School. Lederle Laboratories extends a cordial invitation to all medical technologists to be their guests for a day at the laboratories in Pearl River, N. Y., during the week (June 25-29) following the conference. Transportation to and from New York City will be made available.

FOREIGN

Symposium on Liver Diseases.—A symposium on the pathophysiology, diagnosis, and therapy of diseases of the liver will be held June 29-July 1 at the Medical University Clinic of Freiburg under the direction of Prof. Dr. L. Heilmeyer. Subjects for discussion will include: Tests of the Liver Functions, Pathologic Morphology, Urobilin and Bilirubin Metabolism, and Therapy.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Various Centers. June 19-20 (Parts I and II); September 4-5 (Part I). Candidates may file applications at any time but they must be received at least six weeks before the date of the examination for which application is made. New candidates should apply by formal registration; registered candidates may notify the board, indicating desired location, date and candidate number. Ex. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia 4.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 19-21. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ARIZONA:* *Reciprocity.* Phoenix, July 18-20. Sec., Dr. D. W. Melick, 411 Security Bldg., Phoenix.

CALIFORNIA: *Examination.* San Francisco, June 25-28. Exec. Sec., Mr. Wallace D. Thompson, 1020 N St., Room 536, Sacramento.

CONNECTICUT:* *Examination.* Hartford, July 10-12. Sec., Dr. Creighton Barker, 160 St. Ronan St., New Haven.

DELAWARE: *Examination.* Dover, July 10-12. *Reciprocity.* Dover, July 19. Sec., Dr. Joseph S. McDaniel, 229 S. State St., Dover.

FLORIDA:* *Examination.* Miami Beach, June 24-26. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

GEORGIA: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 111 State Capitol, Atlanta 3.

IDAHO: *Examination, Reciprocity and Endorsement.* Boise, July 9-11. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Examination and Reciprocity.* Chicago, June 19-21 and Oct. 9-11. Supt. of Regis., Mr. Frederic B. Selcke, Capitol Building, Springfield.

INDIANA: *Examination.* Indianapolis, June. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

LOUISIANA: *Homeopathic.* Subject to call. Sec., Dr. F. H. Hardenstein, 903 Pere Marquette Bldg., New Orleans 12.

MAINE: *Examination and Reciprocity.* Augusta, July 10-11. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 19-22. Sec., Dr. Lewis P. Gundry, 1211 Cathedral St., Baltimore.

MARYLAND: *Homeopathic. Examination.* Havre de Grace, June 25-27. Sec., Dr. Robert H. Reddick, R.D. #2, Cambridge.

MASSACHUSETTS: *Examination.* Boston, July 10-13. Sec., Dr. Robert C. Cochrane, Room 37, State House, Boston.

MISSISSIPPI: *Examination.* Jackson, June 25-26. *Reciprocity.* Jackson, June 27. Asst. Sec., Dr. R. N. Whitfield, Old Capitol, Jackson.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 2-3. Sec., Dr. S. A. Cooney, 7 West 6th Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 18-20. Director, Bureau of Examining Boards, Mr. Husted K. Watson, 1009 State Capitol Bldg., Lincoln.

NEVADA: *Examination.* Carson City, July 4-5. *Reciprocity.* Reno, July 3. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

NEW HAMPSHIRE: *Examination and Reciprocity.* Concord, Sept. 12-13. Sec., Dr. John S. Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 19-22. Sec., Dr. Patrick H. Corrigan, 28 W. State St., Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York City and Syracuse, June 26-29. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Reciprocity.* Blowing Rock, July 27. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 11-13. *Reciprocity and Endorsement.* Grand Forks, July 14. Sec., Dr. C. J. Glaspel, Grafton.

OREGON:* *Examination.* Portland, July 16-17. Ex. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 9-12. Acting Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, July 5-6. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 25-26. Sec., Mr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Custer, July 17-19. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 18-20. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 11-13. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

WASHINGTON:* *Endorsement.* Seattle, July 15. *Examination.* Seattle, July 16-18. Sec., Mr. Edward C. Dohm, Olympia.

WEST VIRGINIA: *Examination.* Charleston, July 16-18. *Reciprocity.* Charleston, July 20. Sec., Dr. N. H. Dyer, State Office Bldg. No. 3, Charleston.

WISCONSIN:* *Reciprocity.* Madison, Spring; *Reciprocity and Examination.* Milwaukee, July 10-12. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., Madison.

ALASKA:* On application in Anchorage, Fairbanks, Juneau and other towns. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

HAWAII: *Examination.* Honolulu, July 9-10. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: *Examination and Reciprocity.* Tucson, June 19. Sec., Mr. Herbert D. Rhodes, University of Arizona, Tucson.

DISTRICT OF COLUMBIA: *Examination.* Washington, Oct. 22-23. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., N.W., Washington.

IOWA: *Examination.* Des Moines, July 10. Sec., Dr. Ben H. Peterson, Coe College, Cedar Rapids.

NEVADA: *Examination.* Reno, July 3. Sec., Dr. Donald S. Cooney, Box 9005, University of Nevada, Reno.

NEW MEXICO: *Examination and Endorsement.* Santa Fe, July 15. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

OKLAHOMA: *Examination and Reciprocity.* Oklahoma City, Sept. 28-29. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, June 2, Sept. 8 and Dec. 1. Dr. Earl M. Pallett, Sec., State Board of Higher Education, Eugene.

RHODE ISLAND: *Examination.* Providence, Aug. 29. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

TENNESSEE: *Examination.* Memphis, July 2-3. Sec., Dr. O. W. Hyman, 62 S. Dunlap St., Memphis 3.

TEXAS: *Examination.* Austin, October. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WASHINGTON: *Reciprocity.* Seattle, July 10. *Examination.* Seattle, July 11-12. Sec., Mr. Edward C. Dohm, Olympia.

WISCONSIN: *Examination.* Madison, Sept. 21. Final date for filing application is Sept. 13. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

ALASKA: *Examination and Reciprocity.* Anchorage and Juneau, first week of February, April, June, August and November. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

*Basic Science Certificate required.

DEATHS

Drinker, Cecil Kent, Falmouth, Mass.; born in Philadelphia March 17, 1887; University of Pennsylvania School of Medicine, Philadelphia, 1913; assistant in pharmacology at his alma mater, 1913-1914; in 1917 became acting head of the department of physiology at Harvard Medical School, Boston, where he was later assistant professor, associate professor, and professor of physiology; from 1923 to 1948 professor of physiology at the Harvard School of Public Health, where he was assistant dean from 1924 to 1935 and dean from 1935 to 1942; lecturer in physiology at the Cornell University Medical College of New York City, 1948-1949; emeritus member of the American Society for Clinical Investigation; member of the Association of American Physicians, American Public Health Association, American Physiological Society, Royal Danish Academy of Science and Letters, Phi Beta Kappa, Alpha Omega Alpha, and Sigma Xi; member of the Massachusetts Public Health Council from 1943 to 1946; formerly on the staff of the Boston City Hospital; for many years associate editor of the *Journal of Industrial Hygiene and Toxicology;* author of "The Clinical Physiology of the Lung" and others; served as consulting physiologist for the U. S. Navy; in 1933 received the honorary doctor of science degree from Haverford (Pa.) College and in 1942 the honorary degree of master of arts from Harvard, where in 1955 his portrait was unveiled in the Henry Pickering Bowditch Library; died in the Barnstable County Sanatorium, Pocasset, April 14, aged 69, of bronchopneumonia and arteriosclerotic heart disease.

Skipp, William Marshall ⊕ Youngstown, Ohio; born in Pittsburgh April 10, 1893; Ohio State University College of Medicine, Columbus, 1918; member of the founders group of the American Board of Surgery; member of the House of Delegates of the American Medical Association in 1938 and from 1942 through 1955; past-president of the Ohio State Medical Association; for many years secretary of the Mahoning County Medical Society, of which he was later vice-president and president; served as councilor of the Sixth District; fellow of the International College of Surgeons and the American College of Surgeons; member of the Endocrine Society and the American Goiter Association; past-president of the alumni association of the Ohio State University College of Medicine; founder and for many years chairman of the Allied Professions Committee of Mahoning and Trumbull Counties; one of the founders and a member of the board of directors of Ohio Medical Indemnity; on the editorial staff of the *Bulletin of the Mahoning County Medical Society;* on the staff of the Mahoning Tuberculosis Sanatorium; consultant of the thyroid division, Youngstown Hospital; died in the south unit of the Youngstown Hospital March 14, aged 62, of coronary occlusion, diabetes mellitus, and pneumonia.

McGoldrick, Thomas Aloysius ⊕ Brooklyn, N. Y.; born in Brooklyn in 1874; Long Island College Hospital, Brooklyn, 1896; vice-president of the American Medical Association, 1947-1948, member of its House of Delegates from 1936 to 1953, and member of the Council on Medical Service from 1944 to 1952; past-president of the Medical Society of the State of New York and the Kings County Medical Society; member of the American Trudeau Society; in 1949 appointed a medical representative of the State Industrial Council; for many years a member of the faculty of his alma mater; during World War II director of the Emergency Medical Service for Civilian Defense; formerly chief surgeon of the police department and for many years police surgeon; for many years medical director of St. Anthony's Hospital, Woodhaven; served as director of St. Peter's Hospital; consulting physician at the Goldwater Memorial Hospital in New York City; consultant at the Mercy Hospital in Rockville Centre, St. Catherine's Hospital, and Unity Hospital; in 1936 awarded an honorary doctor of laws degree from Manhattan College; in 1944 decorated Knight of St. Gregory by Pope Pius XII; died March 8, aged 81.

⊕ Indicates Member of the American Medical Association.

Tinley, Mathew Adrian ⊕ Council Bluffs, Iowa; born in Council Bluffs March 5, 1876; University of Nebraska College of Medicine, Omaha, 1902; fellow of the American College of Surgeons; veteran of the Spanish-American War; served on the Mexican Border, and in France during World War I; retired as a major general of the U. S. National Guard March 5, 1940; later lieutenant general of the Iowa State Guard; military honors included the Distinguished Service medal, the Spanish War medal, the Philippines Congressional medal, the Mexican Border Service medal, the Victory medal, and the French War Cross and Legion of Honor; past-president and vice-president of the American Association of Railroad Surgeons; served as vice-president of the Iowa State Medical Association; vice-president of the National Guard Association in 1932-1933 and president in 1933-1934; in 1932 nominated for Vice-President of the United States by the Iowa delegation at the Democratic National Convention; served on the staff of the Jennie Edmundson Memorial Hospital; died March 11, aged 80, of pneumonia.

Robertson, William Egbert, Philadelphia; born in Camden, N. J., July 1, 1869; University of Pennsylvania Department of Medicine, Philadelphia, 1892; Medico-Chirurgical College of Philadelphia, 1904; at one time associate professor of medicine at the Medico-Chirurgical College of Philadelphia; emeritus professor of theory and practice of medicine and clinical medicine at Temple University School of Medicine, which he joined in 1907; past-president of the Philadelphia County Medical Society; fellow of the American College of Physicians and the College of Physicians of Philadelphia; an associate member of the American Medical Association; specialist certified by the American Board of Internal Medicine; formerly medical chief and president of the medical board at Philadelphia General Hospital; on the visiting staff at St. Luke's and Children's Medical Center; medical consultant for Northeastern Hospital, where at one time he was appointed medical director; died in the Philadelphia Home for Incurables March 9, aged 86.

Duncan, Cameron, Brooklyn, N. Y.; born in 1875; Bellevue Hospital Medical College, New York City, 1898; clinical professor emeritus of obstetrics and gynecology at the State University of New York College of Medicine, New York City; specialist certified by the American Board of Obstetrics and Gynecology; member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and the Medical Society of the State of New York; fellow of the American College of Surgeons; past-president of the Brooklyn Gynecological Society and a founder and past-president of the Flatbush Medical Society; consulting obstetrician and gynecologist at Kings County Hospital, Lutheran Hospital, Midwood Hospital, of which he was one of the founders, Flushing Hospital, and Southside Hospital; emeritus obstetrician and gynecologist at St. John's Episcopal Hospital; died in the Midwood Hospital March 4, aged 80, of lung abscess, chronic bronchiectasis, and arteriosclerosis.

Spivack, Julius Leo ⊕ Chicago; born in Odessa, Russia, Oct. 15, 1889; University of Odessa Faculty of Medicine, 1914; clinical associate professor of surgery at the University of Illinois College of Medicine; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; corresponding member of the Mexican Academy of Surgery; entered the service of the Imperial Russian Army during World War I as a captain of the military corps; senior attending surgeon at Mother Cabrini Memorial Hospital; editor of "Urgent Surgery"; author of "The Surgical Technic of Abdominal Operations," now in its fifth edition, translated in Spanish; originator of Spivack's tubovalvular gastrostomy, an operation for formation of an artificial anus, and of other surgical procedures; devised a noncrushing clamp in blood vessel surgery; died in the Presbyterian Hospital March 30, aged 66, of posterior myocardial infarction.

Burwell, Edward Leslie ✠ New Rochelle, N. Y.; born in Brooklyn in 1889; New York Homeopathic Medical College and Flower Hospital, New York City, 1913; served overseas during World War I; one of the founders and past-president of the American Society of Anesthetists, now known as the American Society of Anesthesiologists; a fellow of the American College of Anesthesiologists; past-president of the New Rochelle Medical Association and of the New York Society of Anesthetists; past-governor of the Eastern and Associated Anesthesia societies; member of the International Anesthesia Society; staff member and at one time secretary of the medical board at the New Rochelle Hospital; since 1938 chairman of the board of the New Rochelle Federal Savings and Loan Association; died in the New Rochelle Hospital March 27, aged 66.

Saxton, John Albion, Jr. ✠ St. Louis; born in New Orleans Jan. 29, 1907; Washington University School of Medicine, St. Louis, 1934; assistant professor of pathology at his alma mater; at one time on the faculty of the Cornell University Medical College in New York City; from 1936 to 1938 assistant in animal pathology at Rockefeller Institute in Princeton, N. J.; specialist certified by the American Board of Pathology; member of the American Association of Pathologists and Bacteriologists, College of American Pathologists, American Society for Experimental Pathology, and the American Society of Clinical Pathologists; chief pathologist for the Missouri-Pacific Hospital; director of laboratories for the St. Louis City Hospital; on the staff of the Barnes Hospital; died Feb. 15, aged 49, of cerebral hemorrhage.

Ude, Walter Herman ✠ Minneapolis; born in Willow Creek, Minn., March 19, 1896; University of Minnesota Medical School, Minneapolis, 1925; clinical professor of radiology at his alma mater and the University of Minnesota Graduate School; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, of which he was vice-president, and the American College of Radiology; past-president of the Minnesota Radiological Society; veteran of World War I; on the staff of St. Mary's Hospital; died while vacationing in Honolulu, Hawaii, Feb. 10, aged 59, of coronary occlusion.

Jones, Clarence Porter ✠ Newport News, Va.; born April 7, 1874; University College of Medicine, Richmond, 1895; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; for many years secretary and treasurer of the Seaboard Medical Association; on the staff of the Dixie Hospital in Hampton and the Riverside and Elizabeth Buxton hospitals; died in Locust Hill Feb. 27, aged 81, of congestive heart disease and arteriosclerosis.

Burkard, Adrian Ferdinand, Santa Barbara, Calif.; John A. Creighton Medical College, Omaha, 1902; on the staffs of the St. Francis and Santa Barbara General hospitals; vice-president of the Citizens Savings & Loan Company; died April 3, aged 78, of a heart attack.

Buxbaum, Edward Joseph ✠ Jamaica, N. Y.; Albany (N. Y.) Medical College, 1914; fellow of the American College of Physicians; member of the American Society of Clinical Pathologists; director of the pathological laboratory of the Jamaica (N. Y.) Hospital, where he served one term as president of the board; died in the Long Island Jewish Hospital in New Hyde Park March 30, aged 62, of coronary heart disease.

Carey, Cornelius ✠ Detroit; Detroit College of Medicine, 1910; died in the Veterans Administration Hospital, Dearborn, Mich., Feb. 11, aged 75, of myocardial infarction.

Carter, John Lawrence, Dayton, Ohio; Medical College of Ohio, Cincinnati, 1895; died March 12, aged 84, of coronary thrombosis.

Cerreto, Frank Ronald ✠ Newark, N. J.; Regia Universitá di Napoli Facoltá di Medicina e Chirurgia, Italy, 1934; on the staff of the Columbus Hospital; died in the Hospital for Crippled Children March 28, aged 52, of coronary thrombosis.

Clayton, Edmund M., Albuquerque, N. Mex.; Barnes Medical College, St. Louis, 1899; died in St. Joseph's Hospital March 19, aged 82, of pulmonary infarction and arteriosclerosis.

Cowan, Donald A. ✠ Sault Ste. Marie, Mich.; University of Michigan Medical School, Ann Arbor, 1934; served during World War II; director of the Chippewa-Luce-Mackinac Health Unit; died in March, aged 48.

Czirer, Ladislaus Joseph, Willard, N. Y.; Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest, Hungary, 1912; member of the staff of the Willard State Hospital; died March 10, aged 67, in an automobile accident.

Darrow, Ruth Renter ✠ Chicago; Rush Medical College, Chicago, 1930; on the staff of the Women's and Children's Hospital, where she died April 23, aged 60, of cerebral hemorrhage.

Dooley, John Burrell, Atlanta, Ga.; University of Arkansas School of Medicine, Little Rock, 1908; member of the California Medical Association; an associate member of the American Medical Association; for many years practiced in Compton, Calif.; died March 24, aged 82, of congestive heart disease and stenosis of the aortic valve.

Douds, Edward Hill ✠ Beaver Falls, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1907; served at various times as a member of the city council, the school board, and Chamber of Commerce, of which he was past-president; member of the board of directors of the Citizens National Bank of Beaver Falls; served as a member and president of the staffs of the Providence Hospital and the Beaver Valley General Hospital, where he died March 26, aged 73, of carcinoma of the prostate and rupture of the left ventricle.

Douglass, William Campbell ✠ Tuscaloosa, Ala.; Atlanta School of Medicine, 1909; veteran of World War I; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American Psychiatric Association; in 1925 joined the staff of the Veterans Administration Hospital in Perry Point, Md., and later served at Veterans Administration hospitals in Augusta, Ga., Danville, Ill., Los Angeles, Palo Alto, Calif., and Tuscaloosa, where he died March 24, aged 69, of cerebral hemorrhage.

Drinker, Katherine Rotan, Falmouth, Mass.; Woman's Medical College of Pennsylvania, Philadelphia, 1914; formerly engaged in research and editorial work at the Harvard School of Public Health; died in the Barnstable County Hospital, Pocasset, March 15, aged 66, of acute monocytic leukemia.

Dwyer, Daniel Raymond ✠ Ottawa, Ill.; Loyola University School of Medicine, Chicago, 1927; member of the American Trudeau Society; died in the Augustana Hospital April 4, aged 60, of acute coronary thrombosis.

Dyson, Frank Moir ✠ Philadelphia; Jefferson Medical College of Philadelphia, 1914; served during World War I; died in the University Hospital March 4, aged 64, of dissecting aortic aneurysm.

Edwards, Orange, Seattle; Medical College of Ohio, Cincinnati, 1898; served during World War I; formerly a medical officer in the VA; died March 28, aged 85, of pneumonia.

Ford, Milton, Warfield, Ky.; Louisville (Ky.) Medical College, 1906; member of the county board of health; died in the Logan (W. Va.) Hospital Dec. 24, aged 73, of heart disease.

Gerhard, Walter Bertram, Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; fellow of the International College of Surgeons and American College of Surgeons; on the staff of the American Hospital; consultant, Illinois Masonic Hospital; surgeon emeritus of Columbus Hospital; president of the Northwest Hospital, where he died April 23, aged 72, of urethral obstruction and retroperitoneal sarcoma.

Golinvaux, Cletus Joseph ✠ Bay Harbor Islands, Fla.; St. Louis University School of Medicine, 1921; member of the American College of Chest Physicians, American Trudeau Society, and the Industrial Medical Association; practiced in Monroe, Mich., where he was in charge of the health department in Monroe County; on the staff of St. Francis Hospital in Miami Beach, where he died Feb. 14, aged 59, of cerebral hemorrhage.

Gordon, Samuel Finley ✠ Philadelphia; Medico-Chirurgical College of Philadelphia, 1912; formerly on the faculty of Temple University School of Medicine; served on the staffs of the Frankford Hospital and the Germantown Dispensary and Hospital; died March 12, aged 69, of coronary occlusion.

Gudex, Valentine Arthur ✙ Milwaukee; Milwaukee Medical College, 1895; life member of the Wisconsin Historical Society and the American Public Health Association; for many years deputy state health officer; died Feb. 17, aged 91, of coronary thrombosis.

Harris, Charles Morgan, Jr. ✙ Jersey City, N. J.; Howard University College of Medicine, Washington, D. C., 1924; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; member of the Medical Society of the State of Pennsylvania; on the staffs of the Mercy-Douglass Hospital in Philadelphia, the Community Hospital in Newark, and the Medical Center of Jersey City, where he died March 9, aged 58.

Heisel, Charles Daniel ✙ Cincinnati; Medical College of Ohio, Cincinnati, 1904; fellow of the American College of Surgeons and the International College of Surgeons; past-president of the Cincinnati Academy of Medicine and the Cincinnati Obstetrical Society; a member of the Cincinnati Surgical Society; prior to his retirement served on the staffs of the Deaconess, Jewish, and St. Francis hospitals; died March 25, aged 75, of acute coronary thrombosis.

Henderson, Robert Preston ✙ Orlando, Fla.; Vanderbilt University School of Medicine, Nashville, Tenn., 1917; past-president of the Orange County Medical Society; member of the Southeastern Surgical Congress; served during World War I; at one time an officer in the regular U. S. Navy; served during World War II; on the staffs of the Orange Memorial Hospital and Florida Sanitarium and Hospital; died March 22, aged 62, of coronary disease.

Hibbler, John Arthur, Jr., Kansas City, Mo.; Meharry Medical College, Nashville, Tenn., 1935; member of the Kansas Medical Society; on the staffs of the Douglass Hospital, Kansas City, Kan., and the Wheatley-Provident Hospital; died March 12, aged 48, of intracerebral hemorrhage.

Hobson, Abraham Dana, Huntington Park, Calif.; Washington University School of Medicine, St. Louis, 1908; past-president of the Doniphin County Medical Society in Kansas; served in France during World War I; died March 11, aged 77, of coronary arteriosclerosis and osteoporosis of the spine and pelvis.

Jackson, Howard Colman ✙ Kalamazoo, Mich.; Harvard Medical School, Boston, 1933; specialist certified by the American Board of Surgery; certified by the National Board of Medical Examiners; fellow of the American College of Surgeons; president-elect of the Kalamazoo Academy of Medicine for 1955; served during World War II; chairman of surgical qualifications committee at Borgess Hospital, where he was on the attending surgical staff; on the staff of the Bronson Methodist Hospital; died in Hastings March 21, aged 48, of coronary thrombosis.

Jenkins, Homer L. D. ✙ Hughes Springs, Texas; Chattanooga (Tenn.) Medical College, 1903; member of the American Academy of General Practice; past-president of the Cass-Marion Counties Medical Society; a vice-president of the First National Bank of Lone Star; died March 11, aged 73.

Kiel, Oliver Birdell ✙ Wichita Falls, Texas; Tulane University School of Medicine, New Orleans, 1914; past-president of the Texas State Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; served as chairman of the board of control and chief of medical staff, Wichita Falls Clinic-Hospital; on the staffs of the Bethania Hospital and Wichita General Hospital; trustee of the City National Bank; died Jan. 4, aged 68, of myocardial infarction.

King, Harry Brown, Reynoldsville, Pa.; Jefferson Medical College of Philadelphia, 1895; an associate member of the American Medical Association; on the staffs of the Maple Avenue Hospital and the Du Bois Hospital, where he died Feb. 11, aged 83, of cerebral hemorrhage.

Kunreuther, Max ✙ New York City; Universität Heidelberg Medizinische Fakultät, Baden, Germany, 1909; died March 17, aged 70, of coronary occlusion.

Kuyrkendall, Louis Clifton ✙ McAlester, Okla.; St. Louis University School of Medicine, 1910; past-president of the Oklahoma State Medical Association; served during World War I; died in the Methodist Hospital, Rochester, Minn., March 27, aged 70, of coronary insufficiency and monocytic leukemia.

Leppert, Charles Lynville ✙ Rockford, Ill.; Rush Medical College, Chicago, 1930; member of the American Academy of General Practice and past-president of the Northern Illinois Regional Chapter; member and past-president of the staff of St. Anthony Hospital; died March 25, aged 53, of coronary occlusion.

Levin, Bert G. ✙ St. Paul; University of Minnesota Medical School, Minneapolis, 1924; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; on the staffs of the Children's Hospital, Mounds Park Hospital, and the Midway Hospital, where he died Feb. 8, aged 56, of myocardial infarction and coronary insufficiency.

Lynch, John Charles ✙ Bridgeport, Conn.; University of the City of New York Medical Department, New York City, 1886; also a graduate of a school of dentistry; formerly on the faculty of the New York Polyclinic Medical School and Hospital, and the New York Post-Graduate Medical School and Hospital, Columbia University in New York City; for many years city health commissioner; served on the staff of the Bridgeport Hospital; died March 23, aged 91, probably of acute coronary thrombosis.

McAuliff, George Ralph ✙ Chicago; Rush Medical College, Chicago, 1911; specialist certified by the American Board of Ophthalmology; for many years on the staff of the Illinois Eye and Ear Infirmary; on the courtesy staff of the Wesley Memorial Hospital, where he died April 3, aged 71, of carcinoma of the stomach with metastases to the liver and brain.

McLelland, William Davies, Mooresville, N. C.; Jefferson Medical College of Philadelphia, 1913; member of the Medical Society of the State of North Carolina; veteran of World War I and was awarded the Distinguished Service Cross for heroism in connection with military operation against the enemy; later served in the regular Army; past-president of the Ninth District Medical Society; fellow of the American College of Surgeons; served on the staff of the Lowrance Hospital, where he died Feb. 26, aged 67, of coronary occlusion and pulmonary fibrosis.

Mancuso, Ferdinand ✙ New York City; Baylor University College of Medicine, Dallas, Texas, 1926; died in the Flower and Fifth Avenue Hospitals Feb. 6, aged 55, of generalized peritonitis, incarcerated hernia, and hypertensive cardiovascular heart disease.

Morrison, William Francis ✙ Philadelphia; Jefferson Medical College of Philadelphia, 1896; fellow of the American College of Surgeons; served overseas during World War I; at one time on the staffs at St. Mary's Hospital, St. Vincent's Hospital for Women and Children, and Doctors Hospital; served as police surgeon, as chief physician at the Philadelphia County Prison in Holmesburg, Pa., and on the medical staff of the Baltimore and Ohio Railroad; died in Darby, Pa., March 3, aged 82.

Murphy, Patrick A., Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1905; died in the Cook County Hospital Dec. 21, aged 73, of bronchopneumonia.

Nagel, Joseph Frederick, Ridgecrest, Calif.; University of Cincinnati College of Medicine, 1946; interned at the Lincoln Hospital in New York City; formerly a resident at the Parkland Hospital in Dallas, Texas, and the Veterans Administration Hospital in Hines, Ill.; died in February, aged 37.

Owings, Franklin Davis ✙ Johnson City, Tenn.; Vanderbilt University School of Medicine, Nashville, 1934; served during World War II; member of the American Academy of Dermatology and Syphilology; died March 3, aged 48.

Wilson, John Graham, Factoryville, Pa.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1892; an associate member of the American Medical Association; member of the American Psychiatric Association; served on the staff of the Norristown (Pa.) State Hospital; past-president of the school board; gave "collection of educational museum pieces" to the Factoryville High School; died in Camp Hill Feb. 21, aged 86.

FOREIGN LETTERS

FRANCE

Spontaneous Pneumothorax in Asthma.—J. Turiaf and his co-workers reported in November to the French Society of Respiratory Pathology on 15 patients with asthma in whom air from the lungs entered the pleural and mediastinal spaces. These accidents usually occurred during a violent paroxysm of asthma and took the form of generalized or localized, unilateral or bilateral, pneumothorax with mediastinal and subcutaneous emphysema. Sometimes there was prodromal thoracic pain, but more often the symptoms were masked by those of asthma. In a third of the patients, an effusion was present that was rich in eosinophils, although the general eosinophil count was not increased. The number of patients in whom the accidents occurred represented 0.75% of those with asthma seen by the authors in the course of 10 years. The accidents are generally well tolerated, their effects pass within a few weeks, and the course of the disease then proceeds as usual. Asthma is more important as a cause of nontuberculous spontaneous pneumothorax than has been recognized.

Bronchopyocele with False Cysts.—Magnin and Le Tacon reported at the same meeting that certain bronchopulmonary injuries following compression or perforation of lymph nodes or bronchi after primary tuberculosis are comparable to the middle lobe syndrome. They lose all signs of the causal disease and thus pass into the group of common pulmonary disorders. They may, however, keep on being tuberculous. Bronchopyocele and bronchogenic cysts of tuberculous origin have been grouped together because they may succeed each other chronologically. Anatomically and histologically, nothing differentiates them from nontuberculous cysts as soon as all traces of the causal disease have erased themselves. Clinically, one must differentiate those patients in whom primary infection has been the sole tuberculous antecedent from those in whom tuberculous reinfection has occurred later. In the former the injuries may be inactive sequelae requiring no treatment, while in the latter they harbor tubercle bacilli and must be excised.

Colloidal Radioactive Gold.—At the same meeting, J. Fauvet and his co-workers described their method of palliative treatment of malignant pleural effusions with colloidal radioactive gold. The suspension used is composed of particles with an average diameter of from 50 to 250 millimicrons. Almost all of the dose injected stays in the serosa, which is thus irradiated uniformly over its entire surface. Only a minimal fraction of the Au^{198} penetrates the blood and lymph streams, finally lodging in the lymph nodes, liver, spleen, and bone marrow. Forty patients were treated in this fashion between January, 1952, and July, 1954. Each received one or more doses of about 75 mc. The therapy was well tolerated; the only thing to guard against is an alteration of the blood. The benefit obtained is inconstant and transitory. Best results are obtained after radical excision of the primary cancer, especially if it was in the breast and there is no involvement of the subjacent pulmonary tissue.

Abdominal Pain in Measles.—Abdominal pain may be an early feature of measles, appearing four or five days before the rash; it may accompany the eruption; or it may not appear until convalescence. The localization of the pain resembles that of appendicitis. If the abdomen is opened on suspicion of this condition, the appendix is frequently seen to be congested and the mesenteric lymph nodes may be enlarged. R. Bastin and Cherigie of Paris studied patients with measles by means of the barium enema. In those who had had abdominal pain, there was always some anomaly of the last ileal loop, often of an areolar, or honeycombed, appearance. In children with uncomplicated measles, the mucosa of the ileocecoappendicular region was abnormal in 70%. Mesenteric lymph node enlargement thus appears to be common in measles. It is presumably only a part of a generalized reaction on the part of the lymphatic system. The lungs in measles often show hilar adenopathy and a peribronchial lymphoid reaction. The response of the lymphatic system to the measles virus is nonspecific. We cannot properly speak of "measles appendicitis," but the pain and lesions of the abdominal syndrome complicating measles justify appendectomy.

Tracheotomy in Cranial Traumas.—At a meeting of the Lyon Surgical Society, Wertheimer and Descotes explained that, in patients with severe trauma of the skull, bronchial congestion develops rapidly and is aggravated by hypersecretion of central nervous system origin and by swallowing blood from the nasal fossae. Dyspnea and hypercapnia are engendered by the obstruction, and there is often anoxia as well. Cerebral vasodilatation results, favoring the development of edema of the brain. The dyspnea increases the work of the heart. Neither bronchoscopy nor intratracheal intubation are good methods of combating this obstruction. Tracheotomy, on the other hand, is a simple procedure that can be performed at the patient's bedside and permits evacuation of the secretions, reduces the useless space in the bronchial tree, ameliorates oxygenation, and facilitates tube feeding. Two of five "hopeless" patients were saved in this way.

Acetylsalicylic Acid and Hemostasis.—J. L. Beaumont and his co-workers reported in the *Bulletins et mémoires de la Société médicale des hôpitaux de Paris*, 1955, that acetylsalicylic acid prolongs the bleeding time, not through a direct effect on the blood stream (the amount of prothrombin remains subnormal), but rather through a decrease in platelet adhesiveness. Thus, acetylsalicylic acid may have a hemorrhagic effect, and its use should be restricted in: (1) patients with a bleeding tendency or hemopathy, (2) those with hypertension, (3) those receiving anticoagulant therapy, and (4) those about to undergo an operation, no matter how minor. In any case, no more than 30 mg. per kilogram of body weight should be given.

Lupomas on BCG Vaccination Scars.—A case of lupoma appearing on a BCG vaccination scar had been reported earlier, and Merklen (*Bulletin de la Société française de dermatologie et de syphiligraphie*, 1955) reported two new cases in which the lesions appeared two or three months after formation of the scar. There was no suggestion of exposure to tuberculosis in the prevaccinal or postvaccinal periods and laboratory tests with material from the lesions showed them to be nontuberculous. The development of lupomas in situ is probably just a local reaction to BCG vaccination. The lesions heal in several months.

SWITZERLAND

Protection from Radiations.—The work that the World Health Organization (WHO) might undertake on various aspects of protection from radiation was explored by a study group in Geneva in April. It was recommended that WHO encourage the use of units and standards adopted by the International Commission on Radiological Units. As regards standard isotope sources, WHO could encourage minimum specifications for isotope laboratories and also study means for ensuring that radioisotopes are distributed only to those technically qualified in their use. Moreover, WHO might consider including in the International Pharmacopoeia suitable information on pharma-

The items in these letters are contributed by regular correspondents in the various foreign countries.

ceutical preparations of radioactive substances for use in medicine. Two categories of personnel should be trained in radiological protection: health physicists and physicians. There is a need for more general instruction in radiation problems in relation to health for such other professional groups as sanitary engineers, public health administrators, other health workers, ecologists, and reactor engineers.

Particular attention was paid to the anticipated requirements of physicians in the medical use of radioactivity and in radiation protection. Instruction in these subjects should be included in undergraduate medical curriculums. In addition to the elementary knowledge that all physicians should possess, those who work in industry should be well versed in protection from radiation. Medical personnel should be trained in all countries, especially those new to this type of work, to engage in the use of isotopes for clinical purposes and for research. A varying number of highly trained specialists would be needed in every country to carry out more advanced work and for general advice. Disposal of radioactive waste is the most urgent aspect of the problem. The possible pollution of rivers crossing several countries requires special attention. For this reason, the study group recommended that WHO serve as a clearing house for information on methods of identifying specific radioisotopes in water, soil, or bottom sediments, in flora and fauna, and in body fluids and tissues. It was suggested that WHO might encourage consideration by competent bodies of international disposal areas, where highly radioactive material could be safely dumped.

UNITED KINGDOM

Acute Sore Throat.—A group of general practitioners have collaborated with the London Public Health and the Epidemiological Research laboratories in a survey of the bacteriology and treatment of acute sore throat as seen in general practice (*Brit. M. J.* **1**:705, 1956). Patients more than 2 years old were included in the investigation if their physicians thought them to be suffering from an acute infection of the throat or middle ear of less than 48 hours' duration and of sufficient severity to warrant the administration of penicillin or a sulfonamide. Patients were allocated to one of three treatment groups at random. One group was given potassium penicillin, another sulfamethazine, and the third a placebo, the dose depending on the age of the patient. The range of dosage of penicillin was from 1.2 to 2.4 million units daily and that of sulfamethazine from 2 to 4 gm. daily. These quantities were given in divided doses four times a day for five days. All preparations were given in suspensions of identical appearance and flavor. Each patient was seen three times: on the first occasion, 3 days later, and 10 to 14 days after the beginning of treatment. At each visit, standard nose and throat swabs were taken and sent to the laboratory. Hemolytic streptococci were isolated from 132 of 308 patients (43%); all but four of the strains belonged to group A and were sensitive to penicillin and sulfamethazine. The incidence of symptoms in those patients with negative swabs was just as high as in those with positive swabs. Whereas 61% of patients receiving the placebo were still ill on the third day of treatment, the corresponding rates for those treated with sulfamethazine and penicillin were 38 and 31% respectively. The difference between 61% and the two other rates is significant, but that between 38 and 31% is not. There were, however, fewer failures and relapses in the patients treated with penicillin. The results of treatment were practically the same in the patients with streptococcic and nonstreptococcic sore throats. No clue to the cause of the nonstreptococcic illnesses was found, apart from their apparent response to both sulfamethazine and penicillin. Penicillin and sulfamethazine did not appreciably reduce the duration of illness in the patients under 5 years of age. Possibly the cause of infections in this age group is different or the duration of illness not so readily assessed in those too young to describe their symptoms accurately. Although the clinical efficacy of penicillin was not definitely superior to that of sulfamethazine, it was unquestionably more effective in eradicating hemolytic streptococci, as judged by throat swabs taken on the third day.

Death Penalty.—The bill to abolish the death penalty for murder (the only other offense for which it is enacted is treason) had its second reading in the House of Commons recently, and, provided it is not rejected by the House of Lords, it should soon become law. Murderers found guilty but insane are detained at a criminal asylum, Broadmoor, until they are considered mentally fit for release. Commenting on the new bill, the *British Medical Journal* (March 31, 1956) states that, as a consequence of the abolition of the death penalty, all murderers will receive a nominal life sentence but, in actual fact, a sentence for what is at the time an undetermined period averaging nine years. Medical experts may be called in less often than hitherto, because many murderers will probably prefer not to plead insanity, a device employed in the past to escape the death penalty, since detention in Broadmoor may prove to be longer than a nominal life sentence. Another difficulty is that some murderers, considered mentally abnormal, cannot be fitted into the pattern of insanity designed by the McNaughton Rules of 1843. The McNaughton Rules, which refer only to a defect of reason in the accused person's mind, have long been the subject of criticism by the medical profession. The *British Medical Journal* says that the conception of irresponsibility embodied in them is incomplete in the light of present knowledge. The Royal Commission on Capital Punishment recognized this when it adopted most of the recommendations put to it by a special committee of the British Medical Association and the Royal Medico-Psychological Association. The British Medical Association committee considered that a plea of insanity could be put forward in a case of murder, not only if the accused was laboring under a defect of reason, as recognized by the McNaughton Rules, but also if he had a disorder of emotion such that, while appreciating the nature and quality of the act and that it was wrong, he did not possess sufficient power to prevent himself from committing it. The Royal Commission considered that it would be better to dispense with the McNaughton Rules and leave the matter to the jury or, if that were not acceptable, to consider a modification of the medical association's recommendation.

National Health Service Doctor Criticized.—The father of a deceased patient complained to the Walsall Executive Medical Council, alleging that a physician and his two partners had failed to render proper medical attention to the 17-year-old daughter of the complainant, in that they failed to diagnose acute appendicitis, as a result of which the girl died. She was seen by one of the partners on Jan. 4 and 8 and by another partner on Jan. 9. The patient was admitted to the hospital on Jan. 10 on the advice of a specialist and another physician called in by the complainant, and she died on Jan. 11 after an operation, the cause of death being peritonitis and perforated gangrenous appendix. The chairman of the medical service committee said that the only evidence submitted was that of a wrong diagnosis. The physician had certified the condition to be gastroenteritis, and, although he and the other partner were wrong in diagnosis, they had given the treatment they thought necessary from their diagnosis and had not refused to visit when asked to do so. At a hearing the first partner admitted failing to diagnose appendicitis but maintained that he had exercised that degree of care and skill expected of a general practitioner. Neither he nor the other partner could find any evidence of appendicitis. The father of the patient also alleged that she was examined by a student. In cross examination the physician said that a final-year student did examine the patient under supervision and with her permission and that this was normal practice. The committee hearing the case found that making a wrong diagnosis was not necessarily negligence, nor did it constitute a breach in the terms of service. It found that the onus was on the complainant and his wife for not calling in the doctor earlier when the patient had not improved as expected. It defended the examination of patients by students under supervision. The complainant appealed to the Minister of Health against the council's decision, and the minister has informed the council that in his opinion the physician failed to comply with the terms of service for medical practitioners under the National Health Service, in that his partner and deputy failed to render all proper and necessary treatment.

Health Centers.—Amid the flurry of trumpets with which the National Health Service was introduced in 1948, much was heard of the importance of health centers as the *sine qua non* of general practice. Today they are still notable by their absence and the Minister of Health has just informed the London County Council that he sees no advantage in providing health centers in an area where the existing arrangements for giving service are already adequate. Generally speaking, the only areas in which he sees any scope for health centers are large-scale new housing developments. If health centers are to be established, the minister considers it fundamental that their purpose should be to secure closer association of the local health departments with the general medical services, i. e., general practice. Indeed, except in special circumstances, he will not authorize a new health center unless it is intended for this purpose.

Apart from official policy, the idea of comprehensive health centers has not proved popular among general practitioners. In a letter to the London Executive Council, the London County Council describes some of the difficulties encountered in trying to persuade general practitioners to work in such centers. One of the difficulties raised by practitioners is that there is no protection for the practice of a physician who goes into a health center. If he closes his own office, another physician may set up in practice in the neighborhood. This means that it may be necessary for him to maintain his existing office on moving into the health center and thus incur double expenses. Many physicians have pointed out to the London County Council that the health center should be one of the first buildings erected in a new housing development, so that the incoming residents can find a physician already established on the spot. The council, therefore, concludes that many of the advantages of health centers might more easily and satisfactorily be secured by the evolution of group practices through physicians who choose to work together in premises that they own themselves.

Mastication and Digestion.—Drawing attention to the lack of evidence on the subject of whether mastication is necessary for complete utilization of food, John H. Farrell investigated the problem in 10 healthy adults (*Brit. Dent. J.* **100**:149, 1956). Weighed portions of masticated and unmasticated food were sewed into separate cotton mesh bags, the bags were tied together to insure identical treatment, and then they were swallowed. After passing through the alimentary canal, the bags were recovered from the feces and any food residues that they contained were examined and weighed. A total of 439 experiments were carried out on 29 commonly eaten foods. Of these foods, 18 left large undigested residues in the feces if they were not chewed. These included pork, bacon, beef, mutton, lamb, chicken, potatoes, peas, and carrots. The other 11 foods, including cod, beef fat, kippers, eggs, rice, white and whole-wheat bread, and cheese, were digested easily, whether chewed or not.

The effect of varying efficiencies of mastication were also investigated. Experiments with one subject wearing full upper and lower dentures who had a masticatory efficiency of 50% showed that he was as capable of digesting food as persons with their own teeth and higher masticatory efficiency. In another subject with partial upper and lower dentures, removal of these resulted in a marked fall in masticatory efficiency but did not affect the subject's ability to digest the given foods. In another subject, experiments were carried out that compared the effects of mastication with the posterior teeth on the right side (89% masticatory efficiency) and with the incisors (23% masticatory efficiency); there was no difference in the degree of digestion achieved by the two methods. It is, therefore, concluded that very little chewing is required for maximum digestion and that a person having a masticatory efficiency of 23% may be expected to be able to masticate well enough to digest any of the foods tested.

Immunization in Infancy.—A schedule of immunization starting during the first week of life is suggested by Prof. Wilfrid Gaisford in the April issue of *Practitioner*. His schedule includes the following injections: (1) 0.5 ml. of combined pertussis and diphtheria antigens or pertussis, diphtheria, and tetanus antigens at the end of the first week of life; a second 0.5 ml.-injection at 5 weeks; and a third injection (1 ml.) at 9 weeks (all these injections to be given intramuscularly in the buttocks); (2) BCG given intradermally in the right arm at 3 months and preceded by an intracutaneous tuberculin test using 1:100 old tuberculin; (3) smallpox vaccination at 5 months; and (4) a booster injection of pertussis or combined vaccine at the end of the first year. Steps 1 and 2 should be reversed if there is likely to be any contact with tuberculosis. This reversal also obviates the need for a prevaccination tuberculin test. Professor Gaisford admits that these recommendations represent a departure from the present recognized schedule, but in his experience the scheduled injections have proved practicable, safe, and effective. They provide earlier protection in infancy and are begun while the mother is still under medical supervision and the infant is easily accessible.

Politics and Medicine.—Last year the annual Representative Meeting of the British Medical Association formally requested the council of the association to take such action as would cause the National Health Service to be removed from the political arena. In its report for 1955-1956, the council admits that it has been unable to find a means of implementing this resolution. One of the methods investigated was the replacing of the present central administration under the direct control of the Minister and the Ministry of Health by an independent corporate body. Such a corporate body, however, in the council's view, would be as much under the control of the minister and Parliament as is the present administration. The council also considered the possibility of effecting a gentlemen's agreement similar to that reached in New Zealand, where an assurance has been given by all the political parties that, so far as possible, the health service would not be made the subject of party politics. It was decided, however, that such a scheme would not be feasible in England because it is impossible to divorce the health service, with an annual expenditure in the region of $1,120 million, from parliamentary control.

Higher Education for the Physically Handicapped.—At present there is no grammar school in England solely for physically handicapped children. Although some physically handicapped pupils requiring grammar school education can attend ordinary grammar schools, a few are not able to do so. The existing special schools for physically handicapped children of secondary school age provide only education of a general type. It has therefore been decided to open, at the Lord Mayor Treloar Training College, in Hampshire, a special school for able and gifted physically handicapped boys. This institution is already engaged in training physically handicapped pupils. The new school will accommodate about 70 boys. They will be admitted to the school at any time from the age of 11 years up and will receive a full-time general education up to the age of 16, with some general introduction to technical work. At the age of 16 years, they may transfer to the vocational course. If there appears to be sufficient demand, it is hoped that, as an alternative to vocational training, an advanced academic course for boys likely to profit from it will be developed.

Book of Valor.—The Council of the British Medical Association proposes to recognize acts of heroism on the part of physicians by creating a Book of Valor that will be permanently on view at British Medical Association House, in which particulars of brave acts will be recorded. In each case a copy of the record engrossed on parchment will be sent to the physician or the next of kin. This book will include records of deeds of outstanding valor performed by members of the medical profession in the British Commonwealth and Empire, whether or not they are members of the association.

Poliomyelitis Vaccination.—The figures to date show a wide variation in areas as to the proportion of parents who consent to the vaccination of their children with poliomyelitis vaccine. Thus, acceptances from 29% of parents of eligible children have been received by the London County Council; in the county of Kent from about 33%; in the Yorkshire industrial town of Huddersfield from less than 5%; and in Blackburn, Lancashire, from about 22%.

CORRESPONDENCE

PREMATURE PUBLICITY

To the Editor:—From time to time, members of the medical profession voice complaints regarding "premature publicity" about developments in the field of medicine. These complaints generally are directed at newspapermen and others employed by lay communications mediums. A full examination of the facts would reveal that such criticism is usually groundless. However, it is unfortunately true that some instances of premature publicity do occur now and then, although the National Association of Science Writers (NASW) feels it is achieving considerable success in its persistent efforts to reduce their incidence. In line with this, the NASW wishes to deplore publicly the indefensible methods employed by a certain pharmaceutical firm in connection with the announcement of a new ataraxic drug on Feb. 20, 1956. Early in February, telegrams were sent, on behalf of this firm, to a number of science writers in the United States, which said in part: "By special arrangements with the chief of staff and chief psychiatrist of the (name of hospital and city) you are invited to attend a staff meeting on the results of the hospitals clinical work with a new potent ataractic drug known as . . . . The date is February sixteenth 1:30 p. m. sharp in the medical auditorium of the main hospital building. This is a regular staff meeting to which will be invited physicians from the medical schools of . . . . and . . . . Physicians at (the hospital) have done extensive clinical work with the drug and find it most promising. We thought you would be interested in this significant development in the field of chemopsychotherapy and particularly in the clinical studies under way at the hospital. Transportation incidentals and lunch will be provided by our friends at (name of drug house). Luncheon will be served at the hotel . . . . at 11:30 a. m. sharp. Limousines will leave the hotel at 12:45 p. m. for the hospital."

On Feb. 16, a press release was issued on behalf of this drug house. Dated for use Feb. 20, it was 753 words long and began thus: "A new drug which calms and controls acutely agitated mental patients, alcoholics and drug addicts and facilitates their physical and psychiatric rehabilitation was disclosed here today at a medical staff conference of the . . . . Hospital. The new drug differs from others in use in that the calming of patients is not masked with depression. Little or no fall in the patient's blood pressure has been observed. Vasomotor collapse (precipitous drop in blood pressure) has not occurred, nor has the drug produced tachycardia (excessive rapidity in action of heart). There is no evidence of intolerance to intramuscular nor intravenous administration of the drug, no pain on injection and no tissue destruction at the site of the injection. Jaundice and agranulocytosis attributable to some drugs in the field of chemopsychotherapy has not been observed thus far after administration of the new drug."

Meanwhile, the pharmaceutical house itself was sending confidential letters bearing the name of the firm's president to the profession, which most physicians received on or about Feb. 11. These letters stated in part: "Dear Doctor: You may have read or may be reading in your newspaper about a potent new ataractic drug called . . . . It is almost impossible to control publicity on an important new scientific achievement. Busy reporters are finding out about . . . . in locations where it is being clinically investigated. . . . Because we want you to know about . . . . from us, and not from the newspaper, I am writing you this letter to give you the gist of the preliminary findings. Pre-release publicity is unfortunate because we are not quite ready to make . . . . available."

The NASW feels such duplicity cannot be condoned. It has no place in medicine or in medical journalism.

JOHN TROAN, Chairman
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MUSEUMS OF INTEREST TO PHYSICIANS

To the Editor:—I would like to add some worthwhile sites in European museums of interest to physicians in addition to those outlined by Dr. Frederick Stenn in THE JOURNAL, March 24, page 1090. In Paris, the very modern Palais de la Découverte has an interesting section on medicine. It is located on the Avenue F. D. Roosevelt. Visitors to Germany might be interested in the Deutsches-Gesundheits Museum, Ostmerheimer Strasse 200 in Cologne, West Germany. This museum is the manufacturer of the well-known transparent man and woman. They are temporarily lacking a museum building, but the workshops are well worth visiting. The Dresden Hygiene Museum has been completely rebuilt and with the art treasures returned to Dresden might be well worth a visit. Airplane travelers arriving at or leaving from Prestwick, Scotland, and having time on their hands in Glasgow will find it very worthwhile to visit the Hunterian Museum in Glasgow. The main attraction there is William Hunter's original series of 15 plaster casts of the gravid uterus made in 1750 that served as a basis for his beautiful atlas. An additional attraction for American visitors to this museum is the collection of Whistler's paintings and drawings.

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MEDICAL RESEARCH

To the Editor:—In the Correspondence section of a recent issue of THE JOURNAL **160:**1091 [March 24] 1956), Dr. Israel Davidsohn expressed an idea that should be forwarded to all private foundations and industrial and governmental research agencies with the full endorsement of our medical society. The time has come to stop distributing research money like feather pillows opened on a windy roof top. If medical research is as important as our lip service to it would indicate, opportunity for men entering this field must be provided. Research centers should be built where promising young physicians can enter on the residency level, learn to work with other scientists in the physical, biological, and chemical professions, and learn to use the tools of the trade, the complex instruments, and the libraries that are so costly and so essential to good work. The human body has been subdivided interminably by American Board operations, but I find no American Board of Research. I would no more value a paper on cancer research by one of our "name" surgeons than I would permit a biochemist to remove my appendix. The research scientist must be trained in the fields of biology, chemistry, statistics, and research methods, to name a few. As Jesse P. Greenstein (Biochemistry of Cancer, ed. 2, New York, Academic Press, Inc., 1954) has so aptly put it: "The art of surgery, the insight of pathology, the mastery of radiology and the effective practice of clinical medicine, all require a long and arduous apprenticeship. Standards in these fields are jealously guarded by organized professional bodies, by the watchful scrutiny of highly competent and responsible individuals and by the legal powers of the states. For the most part, these fields are rather watertight compartments, with relatively little overstepping of the boundaries between them and as in all guilds, this exclusive character has tended to promote fine workmanship. Relatively few untrained amateurs or dilettantes have ventured to wander into these disciplines. Yet, for some reason, many of the practitioners of these and other fields, with little or no chemical training have not hesitated to assume a chemical competence. . . . The test tube, no less than the scalpel or microscope is the tool of the skilled workman."

Dr. Davidsohn's suggestion to raise medical research to the dignity of a profession where people can be trained first and receive a decent wage later for the work they do must inevitably

come to pass. I believe, however, that he is wrong in trying to associate research projects with medical schools. They should be set up as distinct research centers where they can get on with the job and get paid for what they do. Medical students are not interested in abstract theory, since 90% of them must absorb the great amount of practical information they will need in practice. A good research man has value per se and should not have to subsidize himself by teaching or taking part-time jobs. To the old saw "you can't buy research" should be added the words "without an organized effort." This nation bought antibiotics, antimalarials, atomic energy, radar, and supersonic aviation simply by putting the men and money together during war time. Unless the medical profession takes some interest in the administration and direction of medical research, it will become a business of the civilian fund raiser or an absolute government function.

I was also impressed with Dr. Davidsohn's suggestion that men over 65 who are seasoned scientists be employed as professors in such research centers. Two years ago I was sitting in a pub in Cambridge, England, and struck up a conversation with an old gent who seemed remarkably well informed. I later learned that he had recently been retired from Cambridge University (on $16 a week!) when he reached age 65. Prior to that he had been a professor of chemistry and many years before had isolated two unknown amino acids and made many great contributions to protein chemistry. Here was a biologically young and brilliant mind, active, experienced, and trained, trying to earn a few dollars a week by teaching chemistry to students who were failing the course. These are the sins of our society that cry to heaven for vengeance.

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POSTANESTHETIC VOMITING

To the Editor:—In their well-documented article on postanesthetic vomiting in THE JOURNAL, Feb. 4, 1956, page 376, Knapp and Beecher conclude that "at the present time it would probably be unwise to adopt therapy with . . . chlorpromazine, 50 mg., for routine use as prophylaxis against postoperative nausea, vomiting, and retching." This is a justifiable conclusion based on their scientific experiment in giving a generous standardized dose of the drug to 152 patients. Unfortunately, it is being interpreted by many readers as if it were an unfavorable report on the drug when used according to the principles of the art of medical practice. This it does not pretend to be. In the art of practice the physician selects the dose individually for each patient, alters his method if results are unfavorable, combines other drugs with it as indicated, and avoids them when they appear contraindicated. In using chlorpromazine in this latter manner, my results have apparently been much more favorable than those of Knapp and Beecher. Up to January, 1956, it was given to 1,077 patients preoperatively and to 459 of these postoperatively. Its use was avoided preoperatively for patients with hypotension from disease, for those with debility, coronary insufficiency, or marked anemia, and for those who were to be in the sitting or semireclining position. Its use was avoided postoperatively for those whose blood pressure had dropped markedly in the operative period, from whatever cause. After a thorough trial with 50 mg., I reduced the preoperative dose to 25 mg. for the young or middle-aged healthy adult weighing 130 to 180 lb. (59.0 to 81.6 kg.). For other patients the dose varied from 10 to 40 mg., depending on their age, weight, and vigor. Scopolamine or atropine was given with it, and in over half the cases Nisentil also was given, in doses of 20 to 40 mg. General anesthesia was usually induced with Pentothal sodium and maintained with ethylene or nitrous oxide, to which were added Nisentil, cyclopropane, or succinylcholine as needed. In other cases spinal anesthesia was used. When used postoperatively, one or two individualized doses of 10 to 25 mg. were ordered at intervals of five hours following the preoperative dose, provided the patient responded to questions and the blood pressure was satisfactory. In this series preoperative sedation was satisfactory; induction of anesthesia was prompt and smooth; there was no trouble with wetness of the respiratory tract nor with tachycardia; and although the blood pressure did tend to fall, sometimes markedly, an intravenous drip of Neosynephrine, when used, was always effective in controlling it (10 mg. or more in 500 ml. of solution). Brewster, a colleague of Knapp and Beecher, has shown that under ether anesthesia the maintenance of normal function of the cardiovascular system depends on the stimulation of epinephrine secretion by ether and that cardiovascular collapse may occur if epinephrine secretion is blocked. Since chlorpromazine inhibits the response to epinephrine and also reverses the action of epinephrine, the wisdom of using it with ether is open to serious doubt. All of their 152 patients had ether, whereas of my 1,077 patients, only 6 had ether as the primary agent and only 21 received it as a subsidiary agent.

Paralleling their findings, in my series postoperative vomiting was reduced far more with chlorpromazine than with seven other drugs and combinations of drugs that were tried in 831 cases. Other undesirable gastrointestinal, circulatory, and respiratory reflexes appeared to be lessened, and patients were in a more comfortable psychic state for the entire operative period than with other types of preoperative and postoperative medication. In association with anesthesia and operation, chlorpromazine seems to have much to offer and seems to deserve further trial to determine the optimal method of use. The difference in the results and conclusions seems to have occurred because the authors carried out a scientific experiment with a generous fixed dosage of chlorpromazine with nitrous oxide and ether, whereas I tried to find out empirically how to get the best results. Conclusions drawn from both methods are of value. The obligation rests on the reader to distinguish between the two types of report and to use judgment in evaluating and applying the conclusions of each.

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REACTIONS TO MEPROBAMATE

To the Editor:—I am writing to you at the request of several of my Southern California colleagues. We have been besieged during the past several months by requests for meprobamate (Miltown and Equanil). Patients we have not seen for years call and demand that one of these be released to them. I would like to report two similar reactions, both occurring within one hour after the first tablet was taken, with both patients being incapacitated and utterly miserable for a period lasting from three to seven days. The first patient, a 59-year-old woman, was severely upset by matrimonial difficulties and experienced severe head and neck pains. After a careful examination, I found her to be suffering from severe nervous tension and Equanil was prescribed, one tablet (400 mg.) in the morning and one in the late afternoon. The patient took her first tablet at approximately 3 p. m., and one hour later experienced severe erythema over the entire body, with associated urticaria and intractable pruritus. There was also a swelling of the fingers and the knees. All types of antihistamine drugs were prescribed but to no avail. After 24 hours, the patient was placed on steroid therapy and responded after three days of treatment. No attempt was made to duplicate this reaction by taking another tablet. The second case was that of a 41-year-old man. Miltown, 400 mg., was prescribed for an anxiety neurosis precipitated by business problems, and, within 15 minutes of taking the first tablet, the patient suffered from a generalized urticaria, swelling of all the small joints, and an intractable pruritus. All types of antihistamine drugs were used with no results, and again steroids were prescribed. After the patient obtained relief, he again took Miltown, but only ½ tablet (200 mg.), and developed a similar and just as intense reaction as before. It was necessary to give steroids for relief.

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MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Albuminuria in Congestive Heart Failure. G. A. Race, C. H. Scheifley and J. E. Edwards. Circulation **13**:329-333 (March) 1956 [New York].

The question whether albuminuria in a patient with congestive heart failure is a reflection of independent renal disease or simply one aspect of the heart failure was investigated in the light of the clinical records and autopsy findings of all the patients at the Mayo Clinic for whom a diagnosis of congestive heart failure had been made during their final illness in the period from 1948 through 1953 and in whom autopsy had been permitted. Four sets of data were obtained covering (1) the various types of heart disease as determined at autopsy; (2) the histological renal findings, which revealed either a renal disorder or normal kidneys; (3) the presence and grades of albuminuria; and (4) gradations of heart failure. These data were derived independently, and then, after all the data had been accumulated, the comparisons were made. Four grades of heart failure were recognized in each of the following disease classifications: (1) mitral-valve disease, with or without aortic stenosis; (2) coronary arterial disease, with or without hypertension; (3) isolated aortic-valve disease; (4) hypertensive heart disease; (5) myocardial hypertrophy of unknown cause; and (6) miscellaneous. Albuminuria was graded according to the standards established by the section of clinical pathology of the Mayo Clinic, which define grade 1 as representing from 5 to 20 mg. of albumin per 100 ml. of urine; grade 2, 30 to 50 mg.; grade 3, 60 to 90 mg.; and grade 4, over 100 mg. The cases (212 in all) were divided into two groups on the basis of the histological findings in the kidneys of each patient; clinically obvious causes of albuminuria had, of course, been eliminated in each case. Group 1 consisted of 161 cases in which the kidneys were either normal or contained lesions of such a nature as not to be responsible in themselves for albuminuria, and group 2 consisted of 51 cases in which the renal lesions might have been responsible for albuminuria. Only the cases in group 1 were used in making the major comparisons in this study.

Albuminuria may be an integral part of the syndrome of congestive heart failure; it was found in 141 (88%) of the group 1 patients. Analysis of the figures showed that the distribution of albuminuria was about equal in the various types of heart disease when heart failure existed and that the degree of albuminuria tended to parallel the degree of heart failure. A fairly close correlation was also found between the degree of albuminuria and the degree of hypertension as revealed by study of the eyegrounds in 21 hypertensive patients. No correlation, however, could be discerned between the degree of albuminuria and either (1) the systolic or diastolic blood pressure values, (2) the known duration of elevated blood pressure, (3) the grades of hematuria, or (4) the blood urea values. No one type of renal lesion was predominantly associated with any one type of cardiac lesion. The severity of the albuminuria discussed in this study is shown by the fact that, although albuminuria associated with cardiac insufficiency is usually said to have a protein content of less than 5 mg. per 100 ml. of urine, the two grades found most often in this series were grade 1, with from 5 to 20 mg. per 100 ml., and grade 2, with from 30 to 50 mg. per 100 ml.

The place of publication of the periodicals appears in brackets preceding each abstract.

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Pyretotherapy and Subcutaneous Hexamethonium in the Treatment of Severe and Malignant Hypertension. P. Thomsen, R. Ortúzar, F. Goñi and others. Circulation **13**:351-359 (March) 1956 [New York].

The effect of combining the subcutaneous administration of hexamethonium with fever therapy utilizing intravenous injections of bacterial vaccines was studied in 12 patients with severe and malignant hypertension presenting the following features: (1) diastolic pressure above 115 mm. Hg not modified by 10 days of bed rest, salt-free diet, and administration of the usual dosage of phenobarbital; (2) progressive impairment of general condition; and (3) vascular damage as shown by changes in the eyegrounds, increase in the size of the heart, and electrocardiographic signs of left ventricular strain with or without signs of myocardial alteration or coronary insufficiency. None of the patients had pronounced renal insufficiency. The pyretogenic substance was Neurovaccine Beta, a water-soluble bacterial suspension containing in 1 cc. 50 million Pseudomonas aeruginosa (Bacillus pyocyaneus), 52.5 million Micrococcus (Staphylococcus) pyogenes var. aureus, and 25 million Bacillus prodigiosus. The hypotensive agents were hexamethonium bromide and chloride. Combination of the two methods of treatment enhances the effects produced by each alone and permits a reduction in dose or frequency of administration by which the undesirable side-effects of hexamethonium and some of the discomfort of fever therapy can be avoided. Hospitalization is necessary, and the patients must be kept under continuous medical supervision.

Treatment was started with the injection of from 10 to 20 mg. of hexamethonium and continued with doses of from 20 to 50 mg. from one to four times in 24 hours. The first parenteral administration of hexamethonium produced sudden and prolonged drops in blood pressure. Subsequent doses, even if larger, had less effect, and the daily pressure curve was highly irregular during this initial period. The pyretogenetic injections were started as soon as the results obtained with hexamethonium were stabilized; in some patients, the febrile crises could be spaced so that they occurred only two or three times a week; aminopyrin was used to alleviate the distress caused by the thermal reaction. Improvement was shown by a marked reduction in blood pressure levels and changes for the better in the eyegrounds, vision, electrocardiograms, cardiac condition, and subjective symptoms. The reduced blood pressure levels, usually stabilized at about 170/90 mm. Hg, have been maintained in certain patients by the oral administration of hexamethonium alone or in combination with Apresoline, and in these patients the disease has apparently regressed to the benign form of hypertension with its more favorable prognosis.

The beneficial effect of the combined treatment seems to be the result of an increased sensitivity to hexamethonium produced by the pyretogenetic injections. This increased sensitivity begins minutes after the injection; it may be marked for as long as seven hours, and it sometimes continues even into the next day. Induction of fever is not necessary to secure lowering of the pressure and potentialization of the effects of hexamethonium, satisfactory results being obtained even when the fever is suppressed with antipyretics. The exact mechanism by which the favorable results are obtained may therefore be related not to the temperature rise but to the injection of foreign protein. The term pyretotherapy would then be less correct than intravenous bacterial proteinotherapy.

Heparin in Cardiovascular Therapy. R. Raynaud. Semaine hôp. Paris **32**:656-659 (Feb. 22) 1956 (In French) [Paris, France].

Heparin is a substance naturally occurring in the body that has a high molecular weight and transports an extremely powerful electronegative charge. As an anticoagulant, it intervenes in a number of stages of the coagulation process; this complex action cannot be measured by simply determining the prothrombin rate.

Heparin plays a part in lipoprotein metabolism in that it mobilizes the beta fraction, converting the slow beta-lipoproteins into fast ones. It is also an antihistaminic. Finally, it seems to have a number of somewhat mysterious properties, e. g., the antiexudative, and these are being experimented with at present. As a therapeutic agent, heparin has two principal indications: thrombosis and atherosclerosis. It is ideal for the treatment of venous thrombosis, but such good results cannot be expected in arterial thrombotic conditions because the lesions are of longer standing and the process is established. Only the intravenous route may be used, and for this to be successful the injection must be repeated every four hours. This method assures constant success in venous thrombosis when 300 to 600 mg. is administered. In arterial and cardiac thrombosis, heparin prevents accidents due to acute ischemia. For the treatment of patients with atherosclerosis, the intramuscular route is just as good as the intravenous. Therapy must be prolonged over a period of months or years and not interrupted for more than one week per month. The injections should be given three times a week and may be supplemented with lipotropic factors. The doses range from 50 to 100 mg.

Frequency of Chronic Cor Pulmonale, Especially Among Patients with Stasis Insufficiency. J. Melchior. Ugesk. laeger **118:** 162-166 (Feb. 9) 1956 (In Danish) [Copenhagen, Denmark].

The term chronic cor pulmonale designates a right-sided heart hypertrophy caused by chronic disorders in the lungs and lesser circulation. The 53 cases of fatal chronic cor pulmonale reported on, in 40 men (34 aged over 50) and 13 women (11 aged over 60), do not differ from case reports previously published as to age and sex distribution, duration of illness, and symptomatology. The most frequent cause was chronic bronchitis and related disorders. Special interest attaches to four cases, three of them in women, where the only or the most important etiological cause was earlier pulmonary embolism. Unrecognized pulmonary embolism was the cause of chronic cor pulmonale in 12 cases, 7 in women, reported by Owen and associates. There is no evidence of increased frequency of chronic cor pulmonale. More frequent diagnosis may be possible if attention is paid to prolonged history of pulmonary symptoms and insufficiency due to stasis. The importance of timely oxygen therapy and other forms of respiratory assistance in patients in whom the cardiac insufficiency is still reversible is emphasized.

The Treatment of Human Pulmonary Tuberculosis with Cycloserine: Progress Report. I. G. Epstein, K. G. S. Nair and L. J. Boyd. Dis. Chest **29:**241-257 (March) 1956 [Chicago].

Cycloserine (Seromycin), a new broad-spectrum antibiotic, was given to 57 patients with pulmonary tuberculosis. A preliminary report of the results obtained with this drug in 37 of these patients was published previously, and the present report gives follow-up data on these patients as well as data on an additional 20 patients treated with cycloserine. Of the 57 patients, 25 had acute pulmonary tuberculosis for which they had not been treated previously, while 32 had chronic pulmonary tuberculosis for which they had been treated with streptomycin, isoniazid, and aminosalicylic acid in various combinations, but without substantial response. Cycloserine was administered orally in doses varying from 1 gm. to 1.5 gm. (20 to 25 mg. per kilogram of body weight) daily, given in four divided doses, for from 5 to 40 weeks.

The results obtained seemed to justify the following conclusions: Cycloserine is an efficient antibiotic agent in the treatment of patients with acute, previously untreated pulmonary tuberculosis. Sputum conversion, clearing of roentgenograms, gain in weight, and restoration of temperature to normal occurred promptly. Cycloserine fills the need for an antimicrobial agent in those patients with chronic tuberculosis who have failed to respond to other drugs, especially patients who are inoperable because of extent of disease or poor general condition. In the daily dose of 20 to 25 mg. per kilogram of body weight given over periods of up to 10 months of continuous therapy, cycloserine elicited few untoward reactions other than epileptiform and psychotic manifestations in known epileptic and psychotic patients. Insomnia, dizziness, sleepiness, hyperirritability, increased reflexes, and involuntary tremors occurred in a few patients but disappeared on continued therapy. Resistance to cycloserine of Mycobacterium tuberculosis has not developed either clinically or in vitro. This is in contrast to other presently available antituberculous drugs. Studies are now in progress to determine the therapeutic compatibility of cycloserine and streptomycin or isoniazid.

Combination of Streptomycin and Chloramphenicol in the Treatment of Pleuropulmonary Suppuration. G. Rossini and E. Sada. Minerva med. **47:**129-134 (Jan. 20) 1956 (In Italian) [Turin, Italy].

The authors have used a combination of streptomycin and chloramphenicol in the treatment of pleuropulmonary suppuration. The quantity of each drug entering into the combination will depend on the species of microflora, the possibility of resistance, and the conditions of the tissues. The results tend to be the sum of those of each individual drug. Streptomycin has an effect on Mycobacterium tuberculosis and on the gram-negative bacteria. Chloramphenicol is effective against gram-negative and gram-positive bacteria, many viruses, and against the Rickettsia. Chloramphenicol diffuses rapidly into the blood. Streptomycin tends to remain in the lung for a long time. The technique of dissolving chloramphenicol for injection has recently been developed. The administration of a combination of streptomycin and chloramphenicol was impossible until recently. This new form of chloramphenicol is highly soluble. Its toxicity is almost insignificant. Direct introduction of the combination into the trachea or into the bronchi is well tolerated. Such is not the case with Aureomycin or Terramycin. In the patients treated by the authors, administration of considerable quantities of the combination has been equally effective either by intramuscular injection or by direct introduction into the bronchi. There were no toxic or allergic reactions. The best results were achieved in recent pulmonary abscesses.

Spreading of Antibiotic-Resistant Staphylococci: Clinical and Therapeutic Consequences. L. Ortona and F. Sorice. Clin. terap. **9:**590-612 (Dec.) 1955 (In Italian) [Rome, Italy].

The authors studied the resistance of micrococci (staphylococci) to antibiotics. Experiments were made with 587 strains of pathogenetic micrococci, and their sensitivity to antibiotics was determined. Personnel and patients of hospitals appear to be the main sources of the antibiotic-resistant strains. Observations were made in three different periods. The resistant strains, those resistant not only to penicillin but to all antibiotics, increased from one period to the other. Streptomycin, chlortetracycline, and oxytetracycline were almost ineffective in the third period. The authors were confronted with a high percentage of isolated strains. The number of chloramphenicol-resistant strains, though smaller, increased progressively during the time of the research. The erythromycin-resistant strains were the least numerous. The presence of antibiotic-resistant strains was higher among patients and hospital personnel than among those who had had no contact with hospitals. The authors suggest the use of combined therapy against antibiotic-resistant micrococci. The choice of the antibiotic must be particularly careful. Sulfonamides are useful. The combination of various antibiotics or of antibiotics with sulfonamides is suggested. Cortisone or ACTH added to the antibiotics can be useful. Artificial hibernation is also suggested. Not too many patients were available for this last treatment.

Sarcoidosis: Pulmonary and Skin Studies Before and After ACTH and Cortisone Therapy. A. Salomon, B. Appel, S. F. Collins and others. Dis. Chest **29:**277-291 (March) 1956 [Chicago].

Of five patients, three women and two men between the ages of 27 and 64 with systemic sarcoidosis involving the lungs, four were treated with corticotropin (ACTH) and one with cortisone for periods varying from 35 to 45 days. Each of the four patients was given 80 units of highly purified ACTH gel intramuscularly daily, and the dose was gradually decreased toward the end of the treatment. The total dose for each varied from 1,500 to 2,000

units. The patient treated with cortisone was given an initial oral dose of 300 mg. daily for the first three days, 200 mg. for five days, and then 100 mg. daily for the remaining 34 days. The total dose was 5,300 mg. The diagnosis was confirmed by skin biopsies in three patients and by lymph node and spleen biopsies in each of the others. Chest roentgenograms, electrocardiograms, skin tests, chemical blood examinations, and pulmonary function studies were carried out before and after treatment. The essential findings in all five patients before treatment were roentgenographic evidence of marked pulmonary involvement, low exercise tolerance, cough, malaise, fatigue, lassitude, and weight loss. Ocular involvement was extensive in two and of moderate degree in one. Skin involvement was not extensive and was limited to the face in two patients and to the arms in a third. Four patients had a positive reaction to the intradermal sarcoidosis (Nickerson-Kveim) test and one had a negative reaction to this test. Pulmonary function studies showed only slight impairment in lung volume measurements compatible with the findings of minimal pulmonary emphysema. The ventilatory reserve was moderately diminished in all patients, but not down to values indicating severe dyspnea, i.e., 70% or less.

The discrepancy between the roentgenograms, which in some patients showed extensive lesions, and the relatively slight impairment of the pulmonary functions was striking. A marked suppressive effect of corticotropin and cortisone on the sarcoidosis lesions was observed in all five patients. In none was the remission complete or equal at all sites of involvement. The lesions of the skin, peripheral lymph nodes, parotid gland, and eyes were most favorably affected. These lesions regressed early in the course of treatment with no significant residua. A pronounced improvement in dyspnea, cough and general well-being was observed in all patients. In nine months' follow-up after cessation of treatment, no relapse occurred with the exception of one patient who, six months after cessation of treatment, had a recurrence of infiltrate over the left malar area at the site of the previous lesions. There was no evidence that the basic, natural course of the disease was altered profoundly or permanently by the treatment with these hormones, but their suppressive effect may be valuable in reducing the damage to vital organs in the course of the active phase of the disease. From the effect of the hormones on the objective symptoms of these patients, it seems reasonable to assume that systemic administration of corticotropin and cortisone accelerates the rate of spontaneous recovery. Adrenocorticosteroid therapy, when practiced with complete laboratory controls and careful clinical observations, may be safely used over a period of from four to six weeks to initiate resolution of the clinically active manifestations of sarcoidosis. Pulmonary changes of sarcoidosis responded more slowly to adrenocorticosteroid therapy, as measured by pulmonary function studies, and to a lesser degree than did skin and other visceral lesions.

Diabetes Insipidus: Five Cases Treated with Vasopressin-Polyvinylpyrrolidone (Insipidin Retard). H. Graudal and S. E. Nielsen. Ugesk. læger **118**:157-160 (Feb. 9) 1956 (In Danish) [Copenhagen, Denmark].

None of the eight cases of diabetes insipidus in children reported was of the hereditary type. One case was assumed to be a sequel of encephalitis complicating epidemic parotitis; the etiology of the other cases was unknown. Five cases were treated with vasopressin-polyvinylpyrrolidone (Insipidin Retard). The diuresis could be regulated to a suitable level by a single daily injection or by injections at intervals of from two to several days. At the same time the general condition improved. The general side-effects after the injection of Insipidin Retard were less marked than after injection of pure extract of posterior lobe of hypophysis. The newer preparations of Insipidin Retard can be given subcutaneously without local symptoms. Patients with congenital diabetes insipidus should not be given hormone treatment, as their daily rhythm is adjusted to the anomaly (Forsmann). In two of the cases described, the dose of Insipidin Retard could gradually be reduced, perhaps because of a similar adjustment. The prognosis is good for untreated patients, but the symptoms are so annoying that treatment is indicated in all acquired cases except the mildest.

Adrenal Cortical Hypofunction (Addison's Disease) in Children: Occurrence in Two Siblings. J. Bie. Nord. med. **55**:193-198 (Feb. 9) 1956 (In Danish) [Stockholm, Sweden].

Not many reports of cases of chronic adrenal insufficiency in children have been published. It occurs more often in boys than in girls and is rarely seen before they reach the age of 10. Hereditary cases have not been reported, but several cases in siblings have been mentioned. The symptoms depend on disturbances in the function of the adrenal cortex. Clinically the symptoms are fatigue, loss of weight, nervousness, characteristic increase in pigmentation of the skin and mucous membranes, anorexia, nausea, and atypical gastric pain, possibly with diarrhea. There is often hypoglycemia and occasionally salt hunger. The Addisonian crisis, acute adrenal insufficiency, is manifested by nausea; vomiting; dehydration; falling blood pressure; a soft, accelerated pulse; and low temperature. Without timely treatment the condition terminates fatally, usually in hyperpyrexia. In the author's two cases, occurring in sisters from a family of six children, the disease started when the sisters were 6 or 7 years old, ran a similar course in each, and was fatal in about three years. Autopsy showed pronounced atrophy or hypoplasia of the adrenals. The increase in height in both children was remarkable. Heart, spleen, and kidneys were found to be abnormally increased in weight, without signs of pathological processes in them. A brother who died at the age of 4 was said to have had symptoms of adrenal cortical insufficiency, but diagnosis was not made. Examination of 23 members of the family failed to reveal any other instances of the disease. Since the production of synthetic hormone preparations the prognosis is considered good, but there is a tendency to permanent emotional lability.

Diabetic Coma: The Value of a Simple Test for Acetone in the Plasma—an Aid to Diagnosis and Treatment. C. T. Lee and G. G. Duncan. Metabolism **5**:144-149 (March) 1956 [New York].

Determinations of acetone in a small amount of oxalated blood obtained from patients with diabetes mellitus were easily performed with commercially available acetone powders or tablets. Results showed that a 4+ reaction to the test indicates a severe degree of ketosis and "chemical coma." The presence or absence of ketosis thus may be promptly determined by this method. When severe degrees of ketosis are present, vigorous treatment with large doses of insulin is indicated. Use of the test during the treatment of diabetic coma gives early evidence of returning insulin sensitivity and helps to prevent overtreatment.

Three illustrative cases are described in a 30-year-old man, an elderly man, and a 56-year-old woman with diabetes mellitus, in all of whom plasma acetone tests were performed. In the young man, who had moderately severe ketosis that responded well to therapy, the initial plasma reaction to acetone indicated that there was a severe degree of insulin resistance and that considerable time would elapse before the effects of therapy would be evident. This proved to be the case. The older man, in contrast to the previous patient, had a higher blood sugar level and carbon dioxide combining power as low as in the first patient, and appeared clinically to be in more profound coma, with impending shock. However, because of the milder degree of ketosis, as indicated on the initial plasma acetone dilutions, he received less insulin; nevertheless, he recovered in less than half the time required by the former patient. The clinical differentiation of the cases of these two patients was difficult, and the blood sugar and carbon dioxide combining power determinations, if taken alone, were confusing. The plasma ketone estimation seemed to be a more reliable guide to therapy than any other examination at the disposal of the authors. The third patient, who had been controlled by 30 units of insulin daily, suddenly became mentally confused; her speech slurred and she complained of pain in the chest. A myocardial infarction was suspected, and glycosuria was permitted as a safeguard against hypoglycemia. Ketosis developed, and the plasma acetone gave a 2+ reaction. An additional 60 units of insulin was given within four hours, but the marked degree of insulin resistance was not appreciated until the next test for acetone in the plasma showed

a 4+ reaction. The original 2+ plasma acetone eliminated diabetic coma as a cause for her confusion and stupor, but subsequent indications of a rapidly increasing degree of ketonemia permitted the administration of large doses of insulin to be given without fear of overtreatment and possible hypoglycemic reactions. Evidence in this patient suggests that the degree of ketonemia is a better guide to the prognosis and treatment of diabetic ketosis than any other single readily available test.

Hematemesis and Melena, with Special Reference to Causation and to the Factors Influencing the Mortality from Bleeding Peptic Ulcers. F. A. Jones. Gastroenterology **30:**166-190 (Feb.) 1956 [Baltimore].

The author presents an analysis of the primary cause of bleeding among 2,011 patients with hematemesis and/or melena who were observed by him over a 14-year period (since 1941) at the Central Middlesex Hospital in London, England. In 101 patients, bleeding occurred after admission to hospital. The 1,910 admissions for bleeding included 340 patients with chronic gastric ulcer, 625 with duodenal ulcer, 118 who had previously undergone gastroenterostomy or gastrectomy, 559 with acute lesions (in whom radiological examination failed to reveal evidence of a definite ulcer two or three weeks after admission), 34 with hiatal hernia, 88 who could not be classified because of incomplete investigations, 39 with gastric carcinoma, 32 (with 52 admissions) with portal hypertension, and 55 with a variety of unusual conditions such as diverticulums, malignant hypertension, uremia, hemophilia, Henoch-Schönlein disease (purpura, arthritis, and abdominal colic), vascular lesions, intestinal tumors, and carcinoma of the pancreas.

Bleeding from portal hypertension due to cirrhosis is regarded as an uncommon cause of admission in London but is a major cause in many parts of the world, including the United States. In this series there were only 52 admissions involving 32 patients. Ten of these patients were over 65 years of age and gave only a short history of symptoms. Twenty-three of the admissions involved patients who had no further bleeding after admission, and bleeding in these cases had almost certainly not been due to gross rupture of a varix but to a small erosion of the esophagus, stomach, or duodenum. It was frequently noted that they had taken aspirin, and it would seem advisable for these patients to avoid the insoluble aspirin tablets. Hepatic coma rather than gross blood loss accounted for one death.

The mortality of patients with proved or probable peptic ulcer was correlated with age, site and size of ulcer, recurrence of bleeding after treatment, clinical complications, and surgical intervention. The mortality shows a sharp increase in patients above 60 years of age; chronic gastric ulcer gives the highest mortality for individual sites—15.9% as opposed to only 2.5% for acute lesions. In the first six years very few patients were operated on, but in the past eight years a policy of surgery in selected cases has been followed in patients with severe continued bleeding or with recurrent hemorrhage after admission, particularly in patients over 40 years of age. Over-all mortality rates were not influenced by this surgical policy, but there was a decrease in mortality in patients under 60 years of age and in patients with chronic gastric ulcer. Patients with hematemesis and melena should be admitted to medical wards, and the ideal professional combination is a keen physician and a somewhat reluctant surgeon. Emergency surgery is advocated in selected cases.

Acute and Chronic Relapsing Pancreatitis: The Clinical Implications of Their Acceptance as Diseases of Adaptation. M. H. Kaplan. Am. J. Gastroenterol. **25:**234-252 (March) 1956 [New York].

As yet, there has been no universally satisfactory and universally applicable explanation of the pathogenesis of pancreatitis. Of all the theories advanced, the theory of impairment of the vascular supply offers the most reasonable explanation of edema, hemorrhage, and tissue necrosis in the pancreas. The vascular concept becomes entirely logical, as well as universal in its application, if pancreatitis is regarded as a disease of adaptation. If pancreatitis is so regarded, the numerous other causes that have been advanced to explain the disease, such as physical trauma, infection, overindulgence in food, and the ingestion of toxic agents, may be regarded as alarm stimuli that trigger the vascular mechanism. Selye's studies on pancreatitis as a disease of adaptation point up the fact that changes similar to those observed in pancreatic disease in man can be produced by stressor agents and that these changes can be prevented by the experimental administration of the glucocorticoid, cortisone.

The clinical implications of acceptance of pancreatitis as a disease of adaptation are both diagnostic and therapeutic. In particular, they suggest the value of an endocrine approach to its management. The patient with chronic relapsing pancreatitis should be protected from stress quite as much as the patient with peptic ulcer. If protective measures are not sufficient, hormone therapy should be instituted, just as it should be used in the acute forms of pancreatic disease. Three cases of acute pancreatitis in two women and one man between the ages of 25 and 45 years were collected from the literature, and nine additional cases of acute and chronic relapsing pancreatitis in patients between the ages of 32 and 75 years are described in which cortisone had been given a therapeutic trial. This method of treatment rescued the patients from impending death. The cases of two of these patients are particularly illustrative. In both, the abdomen was opened; considerable edema of the pancreas and numerous small, ulcer-like lesions covering the omentum and the visceral and parietal peritoneum were observed, and the abdomen was closed without the performance of any surgical procedure. The first of the two patients, who was given cortisone immediately after the surgical intervention, recovered smoothly and promptly. The second patient had a stormy convalescence; administration of corticotropin (ACTH) was entirely ineffective and so was splanchnic nerve block. Recovery after the administration of cortisone was smooth.

Preliminary Report on Treatment of Leukemia with Metacortandracin: Eleven Cases. R. Picard, J. Horeau, U. Guinot and others. Presse méd. **64:**301-302 (Feb. 18) 1956 (In French) [Paris, France].

The authors administered prednisone (metacortandracin) to six patients with acute leukemia, two with lymphoid leukemia, and three with myeloid leukemia. Results were better in the acute than in the chronic cases. Moderate doses of the drug, based on the standard dosage of cortisone in leukemia but corrected for prednisone's greater potency, namely, 30 to 50 mg. per day, were especially effective as regards the general condition of the patient and often restored the temperature to normal. Stronger doses, that is, 100 mg. a day for two or three days, caused important but incomplete hematological remissions in three of the patients with acute disease. All symptoms reappeared on cessation of treatment. It therefore seems that a gradual decrease in dosage to the maintenance level with prolonged therapy is necessary. The authors deemed it prudent to "recharge" the adrenal glands during prednisone therapy and gave injections of corticotropin to their patients, although none had shown signs of adrenal insufficiency. Only one side-effect was observed, and that frequently: it was gastric burning, promptly relieved by bismuth and disappearing spontaneously after the period of high dosage. There was one serious accident: one patient with myeloid leukemia had bloody diarrhea requiring immediate discontinuation of therapy. As in other diseases against which prednisone is effective, the drug is more effective than cortisone in acute leukemia and has the great advantage of not causing water or sodium retention. It is therefore one of the agents of choice for this disease.

Clinical Results with Lente Insulin. M. Protas and W. Kurstin. J. Am. Geriatrics Soc. **4:**117-121 (Feb.) 1956 [Baltimore].

Forty patients with diabetes mellitus were selected from a group with the following conditions: uncontrolled blood sugar levels when treated currently with insulin, thrombotic tendencies, a need for multiple doses of insulin combinations, or allergy to present forms of insulin. These patients were treated with Lente insulin, a protein-free insulin with a prolonged action of the intermediate type. The onset of action of the drug was observed between two and three hours after the injection, with a peak at eight hours. Its effect increased at a slow rate unless a dose

above 50 units was given. The onset of the action of this insulin thus is somewhat more delayed than that of globin or neutral protamine Hagedorn insulins. However, its action is more prolonged than that of either of the other insulins and is not so intense in its nocturnal effect of hypoglycemia as protamine zinc insulin. The fasting blood sugar levels were higher than those observed in the course of treatment with protamine zinc insulin but lower than those usually seen with administration of globin and neutral protamine Hagedorn insulins. Postprandial glycosuria was quite common. Lente insulin was not prescribed in doses above 45 units except in one patient in whom 58 units was used. In some patients it was necessary to split the dose of Lente insulin, giving two-thirds of the total dose before breakfast and one-third before supper. In several patients it was necessary to supplement Lente insulin with regular or crystalline insulin for control of postprandial glycosuria.

Ebstein's Disease. J. W. Brown, D. Heath and W. Whitaker. Am. J. Med. **20:**322-333 (March) 1956 [New York].

Four cases of Ebstein's disease, a congenital cardiac anomaly in which the origin of the tricuspid valve is displaced downward into the right ventricle to divide it into a proximal portion forming part of the atrial cavity and a distal ventricular portion, are described in a 15-year-old boy, in two girls aged 9 and 13 years, and in a 51-year-old woman. Breathlessness on exertion, cyanosis, and palpitation were common symptoms. On physical examination, a precordial systolic murmur and a well-marked triple rhythm at the apex were observed in all four patients. Dulness on percussion to the right of the sternum was observed in two patients. Central cyanosis was present at rest in one patient and during attacks of paroxysmal tachycardia in another. There was electrocardiographic evidence of right auricular hypertrophy in the form of peaked P waves in three and a right bundle-branch block pattern in two. On roentgenologic examination, all the patients had an enlarged globular cardiac shadow caused mainly by the abnormal right atrium. Angiocardiography demonstrated a huge right atrium in all patients and early filling of the left atrium in one patient in whom a patent foramen ovale was subsequently revealed by autopsy. Cardiac catheterization was done in three of the four patients, and in each of them the catheter coiled in a large right atrium, from which it was extremely difficult to pass into the right ventricle and into the pulmonary arteries. The right atrial pressure was raised in two patients; only in one was it possible to catheterize the pulmonary artery, and the blood pressures were normal.

The congenital cardiac anomaly was recognized as downward displacement of the tricuspid valve in all four patients during life, and was confirmed by autopsy in two in whom the characteristic abnormalities of this condition were found. A patent foramen ovale was present in only one of these. The pulmonary vessels were examined microscopically in the 51-year-old woman; the vessels showed only intimal sclerosis, but these changes were regarded as normal for the patient's age. There is at present no indication for surgical treatment of this anomaly.

Congenital Absence of Left Pulmonary Artery. J. Smart and J. N. Pattinson. Brit. M. J. **1:**491-493 (March 3) 1956 [London, England].

A case of congenital absence of the left pulmonary artery is reported in a 30-year-old man. He had no symptoms of any sort. A roentgenogram of the chest showed the left lung to be smaller than the right, and there was a moderate degree of displacement of the heart and mediastinum to the left. Congenital absence of a segment or lobe of the left lung was suspected, but bronchograms showed a normal bronchial tree on both sides. It was also observed that the aortic arch and the upper part of the ascending aorta lay on the right side of the trachea and that owing to the displacement of the mediastinum their shadow was superimposed on that of the spine. The presence of an aortic arch on the right side was subsequently confirmed by a barium meal examination. The angiocardiogram showed absence of the left pulmonary artery, except for a minute branch to the left lung. Bronchospirometry showed that the ventilation of each lung was approximately equal, the vital capacity of the right lung being 2,800 cc. and of the left 2,350 cc. The oxygen uptake on the right side was 390 cc. per minute, while on the left side no oxygen was absorbed.

Absence of one of the pulmonary arteries in itself produces few or no symptoms. In cases where there is no significant cardiac defect, the patient may be asymptomatic or there may be slight dyspnea, cough, or occasional hemoptysis from the bronchial arterial supply to the affected lung. The diagnosis can be suspected from the plain roentgenograms. The presence of a large pulmonary artery, which may even be aneurysmal, on the contralateral side, and the absence of the shadow of a normal pulmonary artery at the hilus on the affected side are important signs. The latter feature may be difficult to appreciate on routine roentgenograms, for the displaced heart may obscure the hilus. Tomograms of the hili are therefore of value. Bronchograms usually show a normal bronchial tree, as in this patient, but in a few cases collected from the literature the affected lung has been small, in one case unilobar and in others agenetic. Confirmation of the absence of one of the pulmonary arteries can be obtained by angiocardiography.

Diagnosis of Central Communications (Shunts) by Continuous Recording of Curves of Concentration of T-1824 with an Ear Densitometer. C. Castillo A., A. Cazorla Monge C. and G. Whittembury M. Medicina **15:**287-294 (Oct.) 1955 (In Spanish) [Buenos Aires, Argentina].

The method of dilution of a dye in the arterial blood for the diagnosis of congenital cardiovascular abnormalities is based on the study of the morphological changes of the curves of arterial concentration of the dye in relation to normal curves. The authors made this test in 72 persons, either normal or with such abnormalities. An ear densitometer was used. The ear was heat-flushed for 10 minutes prior to the injection of 2 cc. of a 1% solution of T-1824 (Evans' blue), which was injected into the antecubital vein. The intravenous injection of the dye was given in a period of no more than 1 second. The curves were normal in 21 out of 22 normal persons. They were typical of left-to-right shunt in 46 out of 47 patients with interauricular or interventricular communication and were typical of right-to-left shunt in three patients with Fallot's tetralogy. There was clinical, electrocardiographic, and roentgenographic diagnosis of such abnormalities. The results of the test were in perfect agreement with the clinical diagnosis. The results of the test can give normal curves of dilution in cases of small septal defects. On the other hand, typical curves of shunt from persistence of the cardiovascular abnormality change to normal when the abnormality is surgically corrected, except in cases in which another cardiovascular abnormality is present. The test is of value for the diagnosis of congenital cardiovascular abnormalities, for the selection of patients for cardiac catheterization, and for the diagnosis of a shunt during cardiac catheterization. The authors recommend the method as a routine for outpatients in heart clinics. The technique is simple, and the procedure is well tolerated. Indigo carmine can be used instead of T-1824 with certain advantages; there is greater facility of elimination through the kidneys, and it does not produce a blue discoloration of the skin of the patient such as T-1824 may produce.

The Antemortem Diagnosis of Syphilitic Aneurysm of the Aortic Sinuses: Report of Nine Cases. C. W. Merten, N. Finby and I. Steinberg. Am. J. Med. **20:**345-360 (March) 1956 [New York].

Diagnosis of syphilitic aneurysm of the aortic sinus was made during life in only one of 19 patients between the ages of 17 and 60 years whose cases were collected from the literature. The aortic sinuses lie deep within the substance of the heart and are inaccessible to physical diagnosis. Nine additional cases of syphilitic aneurysm of the aortic sinuses are described in one woman and eight men between the ages of 45 and 64 years, in whom the diagnosis was established during life by angiocardiography. The findings in the 9 patients were compared with those in the 19 in whom the diagnosis was made on autopsy. Two groups were recognized. Aneurysm of the aortic sinuses was associated with fusiform dilatation (aortitis) of the ascending aorta in six patients, and localized aortic sinus aneurysms

were observed in three. Unlike congenital aneurysms of the sinus of Valsalva, syphilitic aneurysms may be huge and may occasionally rupture outside the heart. Aortic regurgitation was present in eight of the patients; it is an outstanding feature of aneurysm of the aortic sinuses. Next in importance is heart failure, which often may be intractable. Rupture of an aneurysm with creation of an aorticocardiac shunt is characterized by the presence of harsh machinery-like murmur associated with overloading of the chambers at the right side of the heart and the pulmonary arterial system. Rupture of the aortic sinus aneurysm occurred in 11 of the 19 patients; in 8 of the 11, the aneurysm ruptured into the lesser circulation and this rupture was not always immediately fatal, while rupture outside the heart always caused sudden death. Rupture did not occur in any of the authors' nine patients.

The usual electrocardiographic findings of unperforated syphilitic aortic sinus aneurysm are left axis deviation and left ventricular hypertrophy. Roentgenographically, the presence of linear calcific deposits in the ascending aorta is good evidence of syphilitic aortitis; it was present in all but one patient. In several patients the conventional roentgenogram also revealed calcification in the intracardiac portion of the ascending aorta and often clearly outlined the dilated aortic sinuses. Angiocardiography demonstrates the aneurysms and their effects on the adjacent cardiovascular structures. The prognosis of syphilitic aneurysm of the aortic sinuses is not necessarily unfavorable. Of the nine patients, three were lost to observation, and of the six who were followed up for five years, two died and four are alive.

SURGERY

Cerebral Embolism in the Course of Mitral Commissurotomy: Experimental Research Studies on a Technique Capable of Preventing Cerebral Embolism During Interventions on the Heart. R. Caminiti. Policlinico (sez. chir.) **63:**32-42 (Feb.) 1956 (In Italian) [Rome, Italy].

A series of experiments was undertaken on dogs in an attempt to determine the usefulness of compression of the carotid arteries at the neck to prevent cerebral embolism during interventions on the heart. Thrombi, which were prepared by different methods, were injected into the left atrium, the left ventricle, or the ascending aorta of the animals. In one instance, a radiopaque thrombus was injected into the left ventricle and its course was followed on the roentgenograms. In the dogs whose carotid arteries were not compressed during the injection of the thrombi, these entered the carotid arteries and subsequently became localized in the brain. No cerebral embolism was found in the dogs in which the carotid arteries were compressed at the neck during the injection of the thrombi.

Caminiti states that this method can be used effectively to prevent the much-feared cerebral localization of emboli during commissurotomy on the mitral valve in man. He reports on two patients with mitral stenosis associated with atrial fibrillation in whom this technique prevented the occurrence of cerebral embolism during a commissurotomy. Signs of embolism did appear in one of them at the aortic bifurcation, but he recovered completely after an embolectomy was performed. The other patient showed signs of occlusion of the radial artery. Numerous commissurotomies have been performed at the Institute of Surgical Pathology of the University of Rome in patients with mitral stenosis. Compression of the carotid arteries at the neck during the intervention prevented the occurrence of cerebral emboli in most of them. When signs of embolism did appear, the emboli were located in the peripheral organs or tissues.

Experimental Treatment of Ventricular Fibrillation by Means of Electrical Defibrillation in Animals. H. Burmeister. Arch. klin. Chir. **281:**390-404 (No. 4) 1956 (In German) [Berlin, Germany].

In earlier experimental investigations on the treatment of ventricular fibrillation in dogs with chemical substances, Burmeister had obtained information on the combating of asystole, on the reoxygenation of the heart, and on the effective restoration of circulatory heart action. The studies described were concerned with the use of the electrical defibrillator in 30 defibrillations on 10 dogs ranging in weight from 12.5 to 25.5 kg. (27½ to 56 lb.). The ventricular fibrillation could be counteracted in all 30 experiments by from one to five electric shocks. From 1.5 to 1.7 amp. of alternating current were required to restore regular heart action.

Good oxygenation of the myocardium is a prerequisite for the success of electrical defibrillation. Atonic fibrillation must be transformed into the tonic form by cardiac massage before electrical defibrillation is attempted. The author found single electrical shocks lasting from one-half to one second more effective than serial shocks (five shocks in one and one-half seconds). After the use of substances that increase irritation, such as epinephrine or calcium chloride, defibrillation could be effected with the same current intensities provided cardiac massage was carried out for two minutes after the injection of these substances. Novocaine amide did not interfere with defibrillation. Ventricular fibrillation developing after venous or arterial air embolism could likewise be counteracted by electrical defibrillation, when the use of the defibrillator was preceded by cardiac massage. The advantages of electrical as compared to chemical defibrillation consist in the more rapid return of orderly heart action with preservation of the cardiac tonus.

Primitive Chondrosarcoma of the Lung. F. Cecconi. Arch. ital. chir. **80:**218-231 (No. 3) 1956 (In Italian) [Bologna, Italy].

Chondrosarcoma can be so defined only if the following characteristics are present: a growth that is malignant from the clinical and morphological points of view and a disordered and atypical proliferation of elements similar to those present in cartilaginous tissues. The process is malignant if microscopic and macroscopic observations show invading proliferation, metastatic activity, and a cartilaginous tissue that is rich in cells and highly atypical. The author, in a study of eight cases, noticed that seven times out of eight the neoplasm was located in the left lung. This, he points out, is not the case with cartilaginous tumors of the lungs, which appear with equal frequency in both lungs. The clinical aspect of primitive chondrosarcoma of the lung is similar to that of malignant neoplasms of the lungs. Only the histological examination makes possible the proper diagnosis. The radiological examination seldom helps in establishing a specific diagnosis. Bronchoscopic examination gives negative results, since the chondrosarcoma seldom infiltrates the bronchial walls.

A Concept of the Etiology of Gastric and Duodenal Ulcers. L. R. Dragstedt. Gastroenterology **30:**208-220 (Feb.) 1956 [Baltimore].

Dragstedt summarizes the evidence that duodenal ulcers are usually due to a hypersecretion of gastric juice of nervous origin, pointing out that this concept is supported by the fact that patients with duodenal ulcer regularly secrete from 3 to 10 times as much gastric juice in the fasting stomach as do normal people and the further fact that a hypersecretion of gastric juice of this degree regularly causes duodenal ulcers if reproduced in experimental animals. The abolition of this fasting hypersecretion in duodenal ulcer patients by gastric vagotomy indicates that it is of nervous origin. The prompt healing of the ulcers when the hypersecretion has been abolished by vagotomy constitutes final proof that the lesions are produced and maintained by a hypersecretion of gastric juice.

The concept that gastric ulcers are due to a hypersecretion of gastric juice of hormonal origin dependent upon prolonged or excessive liberation of the gastric secretory hormone, gastrin, is supported by the following evidence. A hypersecretion of gastric juice due to excessive or prolonged liberation of gastrin can be induced in dogs by the transplantation of the antrum of the stomach into the colon as a diverticulum. This hypersecretion is sufficient in degree to produce typical ulcers in previously normal mucosa. Stasis of food in the stomach, either as a result of pyloric stenosis or gastric atony, can cause a hypersecretion of gastric juice of humoral origin sufficient in degree to produce gastric ulcers in experimental animals and in man. The response of gastric and duodenal ulcers to gastric surgery supports these

concepts of their origin. Thus, complete gastric vagotomy has been found effective in the treatment of duodenal ulcers, but not in gastric ulcers. Antrum resection, which abolishes the humoral phase of gastric secretion, is followed by a high incidence of marginal ulceration when done for patients with duodenal ulcer, but is rarely followed by this complication when done for patients with gastric ulcer. Gastroenterostomy, which relieves the stasis of food in the stomach, is seldom followed by marginal ulceration when done for gastric ulcer but is frequently followed by marginal ulceration when done for the treatment of duodenal ulcer.

Uropepsin Excretion Studies in Clinical Surgery. A. H. Levy and S. Levine. Gastroenterology **30:**270-278 (Feb.) 1956 [Baltimore].

Uropepsin is the name for the proteolytic enzyme found in the urine of normal persons and of many animals. The substance probably exists in the blood and in normal urine as pepsinogen. In a pH medium of about 1.5 it assumes proteolytic properties almost identical with those of gastric pepsin. It has been reported that uropepsin is excreted in amounts closely proportional (about 1%) to the amount of pepsin secreted by the stomach. It is also said that the 24-hour uropepsin excretion rate is relatively constant for each individual and that the average output varies in disease states in the same way that the output of gastric pepsin does. Of particular interest in patients undergoing surgery is the fact that the enzyme is secreted directly into the bloodstream. It is therefore not inactivated by the reflux of intestinal juices into the stomach as is the case with hydrochloric acid. It is also important that uropepsin samples can be collected without causing discomfort to the patient and that the total daily output can be measured over long periods of time.

The excretion of uropepsin was studied before and after operation in 15 patients with peptic ulcer, and data were also collected on 11 other persons. The authors were primarily interested in determining whether the uropepsin test, as performed under ordinary clinical conditions, was a useful index of gastric secretory activity in patients undergoing surgery. They found that it was not. They were unable to detect a consistent excretion pattern before or after operation. Vagotomy, though adequately performed as judged by other criteria, had no demonstrable effect on uropepsin excretion levels. In a very general way, gastric resection was followed by a decrease in the average uropepsin excretion. The decrease was not, however, proportional to the amount of stomach tissue removed. The ability to excrete to or beyond the preoperative levels was retained by some of the patients. Reviewing the literature on this problem, the authors find that many papers report findings similar to their own. They feel that the results are explained most easily by the assumption that uropepsin excretion is not directly proportional to gastric secretion. There is the possibility, however, that some other factor is quantitatively more important than local stimulants, vagus effect, or the amount of functioning gastric tissue present. Simultaneous measurements of steroid and uropepsin excretions are suggested.

Cancer of the Stomach: A Report on Cases Treated by Total Gastrectomy. H. K. Ransom. Gastroenterology **30:**191-207 (Feb.) 1956 [Baltimore].

The records of 118 patients in whom gastrectomy was performed at the University of Michigan Hospital were reviewed. The lesions requiring the operation were chiefly cancer, with an additional small group of benign lesions that for the most part were gastric ulcers mistaken for carcinoma at operation. The series was divided into two groups: those operated on between 1937 and 1947 and those operated on from 1947 to 1954. In 1948, a report was presented on 68 patients, and in this paper data are presented concerning 50 additional cases in which total gastrectomy was performed between September, 1947, and January, 1954. The follow-up studies extended into early 1955. The over-all mortality rate has decreased slightly, from 20.6% in the earlier series to 18%, and for carcinoma it has fallen from 20.3% to 16.3%. Operative deaths were due to separation of the esophagointestinal anastomosis in most cases, as demonstrated at autopsy.

The combined abdominothoracic incision is superior to all others. Because of better exposure obtained with it, a more secure anastomosis may be made. Involvement of the lower portion of the esophagus is frequently encountered, and only by a thoracic approach can this be adequately dealt with. Experience with esophagoduodenostomy is too meager to warrant conclusions. Esophagojejunostomy with a large enteroenterostomy is at present most commonly employed. For a high anastomosis, e. g., above the diaphragm, the Roux-Y technique has advantages. The curability of cancer as judged by postoperative survival time was less in period 2 than in period 1. The explanation undoubtedly lies in the fact that during period 2 a larger number of patients with far-advanced or unfavorable lesions was accepted for operation. That clinical cure of cancer is possible by means of total gastrectomy is evidenced by the fact that one patient lived for nearly 8 years after operation, finally dying of intercurrent disease, and three patients are now living 5½, 12, and 16 years after operation.

Total gastrectomy is not considered a suitable procedure for palliation. The combination of symptoms due to recurrent cancer plus those of the postgastrectomy syndrome cannot be considered an amelioration. Possible exceptions are found in patients with obstruction at the esophagogastric junction and those with severe hemorrhage. Until more long-term survivals are obtained than in the past, it does not seem justifiable to subject all persons to a procedure with high mortality and postoperative morbidity for the possible benefit of the very small number who are destined to survive for some time. At the present time there is no convincing evidence that total gastrectomy for all patients with gastric cancer would yield better results than can be obtained from radical subtotal resection. But total gastrectomy is feasible technically and physiologically and has a place in the treatment of gastric malignancy. The number of benign lesions requiring complete gastrectomy is small. If in the future substitution grafts prove effective, their field of greatest usefulness should be in such benign cases.

Indications and Results of Surgical Treatment of Gastric Cancer: Clinical and Statistical Considerations on 356 Cases. A. Bellavia and M. Mancuso. Policlinico (sez. chir.) **63:**43-63 (Feb.) 1956 (In Italian) [Rome, Italy].

A total of 356 patients (248 of them men) with cancer of the stomach was seen by the authors from October, 1946, to March, 1954. Operation was not performed in 30 (8.4%) because of the presence of diffuse liver or peritoneal metastases or of large tumors in the abdomen. An exploratory laparotomy was performed in 101 (28.2%), palliative surgery (gastroenterostomy or gastrostomy) in 27 (7.5%), and radical surgery in 198 (60.7%). In the last-named group, 96 underwent a total and 102 a subtotal gastrectomy. Cancers located high in the stomach were approached by the abdominothoracic route, whereas antropyloric cancers were reached through the abdominal route. The over-all postoperative mortality was 12.9%, whereas for radical intervention it was 17.6%. Causes of death were cardiac insufficiency, cardiohepatorenal insufficiency, pulmonary embolism, peritonitis, and postoperative shock. Dehiscence of the esophagojejunal anastomosis was observed in only 12 of the 96 patients in whom a total gastrectomy was performed.

The late results were evaluated separately in the patients who submitted to operation from 1947 to 1949 and in those operated on from 1950 to 1954. A comparison indicated that the results of surgical treatment of gastric cancer have improved. The mortality rate for subtotal gastrectomy decreased from 10.8 to 9.8% and that for total gastrectomy from 25 to 23.9%. These improvements were the result of greater experience on the part of the surgeons, improved assistance during and after the operation, and availability of blood banks and means of resuscitation. Total gastrectomy should be considered the treatment of choice for gastric cancer. Subtotal gastrectomy gives good immediate and late results in aged patients and in patients with antropyloric gastric cancer.

Anemia After Total Gastrectomy (Experiments in Prevention and Treatment). O. Rainer and S. Zollner. Arch. klin. Chir. **281:** 371-381 (No. 4) 1956 (In German) [Berlin, Germany].

Fifty-nine patients who had been subjected to total gastrectomy were studied with regard to the development of anemia. At most, four years had elapsed since the operation, and pernicious anemia developed in only one patient three years and five months after the gastrectomy. The authors feel that this is largely due to the postoperative prophylactic administration of vitamin B_{12}, the patient being given intramuscular injections of 30 mcg. of vitamin B_{12} at two-week intervals. The patient in whom pernicious anemia developed had discontinued this prophylactic treatment two years before. The authors prefer the parenteral administration of vitamin B_{12} to its oral administration, because they feel that the orally administered vitamin B_{12} will be largely destroyed in the upper small intestine of gastrectomized patients because of the presence of bacilli in the colon.

In order to obtain information on the development of sideropenic (iron deficiency) anemia, the authors studied the iron metabolism after gastrectomy. They found that, if the mucosa of the small intestine is not damaged, adequate enteral resorption of ferrogluconate is possible even in the absence of free hydrochloric acid. If an iron deficiency anemia has developed, it can be effectively treated by the oral administration of an ionizable iron preparation in the form of ferrogluconate. They recommend a continued oral iron therapy after gastrectomy. If atrophic changes develop in the small intestine or if the capacity of the plasma to bind iron is reduced because of deficiency or blockage of the metal-binding beta, globulin, the authors resort to the intravenous administration of ferric-saccharate. If sideropenia is treated early, while it is still masked, there is a possibility that atrophic changes in the small intestine will be prevented or at least retarded. The authors also call attention to the importance of vitamins in erythropoiesis and in epithelial and cellular protection. For this reason they recommend the prophylactic administration of vitamin C and B_2 complex.

Clinical Study and Therapy of Portal Hypertension. J. Govaerts, A. Van Wien and R. Kiekens. Acta clin. belg. **10:**493-516 (Nov.-Dec.) 1955 (In French) [Brussels, Belgium].

The majority of cases of Banti's syndrome are the result of portal thrombosis; this explains why splenectomy, long considered the treatment of choice, does not prevent relapses in more than half the cases. This operation is curative only when thrombosis is limited to the splenic vein and in the rare cases that can be called Banti's disease, or primary splenic anemia. The proper treatment for Banti's syndrome with portal block is portacaval shunt. This cannnot usually be accomplished directly because the portal trunk is thrombosed, so an end-to-side splenorenal anastomosis is carried out. The kidney is preserved. The mortality from this procedure among patients with extrahepatic block is very low, and the long-term functional results are satisfactory. This treatment modifies portal hypertension and stasis and is therefore more appropriate than direct intervention on esophageal varices. Such methods are reserved for relapses after splenectomy, since a wide anastomosis is no longer possible. Anastomoses between small veins do not give satisfactory results.

Portal hypertension frequently occurs in cases of hepatic cirrhosis. Esophageal varices appear; these are the cause of most hemorrhages from the digestive tract occurring in cirrhotic patients. Portal hypertension probably plays a part in the genesis of cirrhotic ascites. Recent works, however, have placed emphasis on other causal factors, namely, disturbances in sodium and water metabolism. Portacaval shunts constitute definitive treatment for only a small number of carefully selected cases of cirrhotic ascites. They can, however, be of great benefit in preventing the massive hemorrhages that kill 50% of patients with cirrhosis.

Carcinoids: Report of 30 Cases. G. G. Broad. New York J. Med. **56:**705-707 (March 1) 1956 [New York].

Carcinoids are tumors of the intestinal tract arising in the deep layers of the mucosa. They often present themselves as submucosal tumors when they are small. Some of the carcinoid tumors, including metastatic tumors, remain localized for years. Some of them become highly malignant, causing early death. The pathologist has difficulty in diagnosing malignancy in some of the carcinoid tumors because the intracellular structure and the arrangement and formation of the cells into pseudorosettes or other formations in the so-called benign growths and in the so-called malignant carcinoids are essentially the same.

The author adds 30 cases to the literature on carcinoids. Three were observed by himself and the others were found in the files of the medical school and hospitals in Syracuse, New York. The period of time involved is 1940 through 1954. There were nine malignant tumors (30%) in this group: one in the vermiform appendix, four in the ileocecal region, one in the jejunum, and three in the rectum and rectosigmoid junction. The author mentions a report on over 300 cases in which the incidence of malignancy was 37.9%. He agrees with other investigators that all carcinoids have malignant potentialities and that therefore adequate removal is essential. The consensus seems to be that small tumors up to about 1 cm., if noninvasive and not fixed in position, may be safely treated with wide local excision with careful follow-up. The frankly malignant lesion requires radical treatment, as do other forms of carcinoma of the intestinal tract.

Laugier's Hernia. A. Priesching. Arch. klin. Chir. **281:**411-419 (No. 4) 1956 (In German) [Berlin, Germany].

Priesching discusses Laugier's hernia (hernia ligamenti lacunaris gimbernati) on the basis of three case histories. All three cases were studied at autopsy. The patients were women ranging in age from 50 to 61 years. The hernia found in the first of these was typical of Laugier's type. In the other two the hernial ring was in a fibrous plate that merged medially into a typical ligamentum lacunare (gimbernati), and laterally it was defined by a reinforced concave margin against the structures of the lacuna vasorum.

The concept of the ligamentum lacunare is not completely clear. The author reviews its terminology, anatomy, pathology, and clinical aspects. The ligamentum lacunare is not really a ligament or band but rather a fibrous plate. Nevertheless, the author feels that the name should be retained. The clinician will differentiate between ordinary femoral and Laugier's hernia only when the symptoms and therapy of these two types of hernia differ. This is the case to a certain degree if the term Laugier's hernia is applied only to that form of hernia which passes through the medial, dense portion of the fibrous plate. The author applies the term ligamentum lacunare (gimbernati) only to this portion, and he speaks of Laugier's hernia only if the hernia passes through this ligament and lies on the surface of the fascia pectinea. Nothing definite is known regarding subjective symptoms caused by Laugier's hernia. Treatment should consist of reposition of the hernial contents, care of the hernial sac, suturing of the hernial ring, and perhaps splitting of the hernial ring at the lateral rim.

Review of Some Experiments with Freeze-Dried Grafts. W. H. Sewell, D. R. Koth, J. W. Pate and W. C. Bedell. Am. J. Surg. **91:**358-361 (March) 1956 [New York].

Homologous tissue frozen by partial immersion of its container in a mixture of dry ice and alcohol and then sealed in vacuum in small containers was used for subsequent grafting in animal experiments. Freeze-dried homologous arteries were placed in the abdominal aorta of dogs; freeze-dried homologous fascia from the anterior rectus sheath was used to replace large defects in the diaphragm and to repair large ventral hernias surgically created in the abdominal wall of dogs; freeze-dried arteries were used to form sheaths around injured tendons; freeze-dried dura mater grafts and freeze-dried homologous bone grafts were used as replacement for their respective tissue in dogs; attempts were made to use segments of freeze-dried tissue to replace visceral tubes such as the esophagus, the common bile duct, and the ureter in dogs. Comparable fresh and freeze-dried split-thickness homologous skin grafts were implanted in surgically created full-thickness skin defects on dogs and rabbits. Successful results were obtained with arteries used for arterial replacement and as tendon sheaths. Freeze-dried bone and dura functioned satisfactorily as replacements for their respective

tissue. Fascia was satisfactory for the repair of ventral hernias. Preserved esophagus and artery failed when used as esophagus. Arteries failed in common bile ducts and ureters. Fascia failed in the diaphragm. Freeze-dried homologous skin sloughed at approximately the same time as viable homologous skin.

These results showed that the process of preserving homologous tissue by freeze-drying for subsequent grafting has certain practical advantages but also has important limitations. Freeze-dried grafts of some types of tissue result in less host-tissue reaction than is seen with comparable fresh grafts. The cells are dead, and the process is useful when mechanical function only and not metabolic activity is required of the grafted tissue. The grafts were generally successful when they were implanted in an area in which they could be replaced readily by host fibroblasts and in regions free from bacterial contamination and irritating chemicals. When these criteria were met, the freeze-dried grafts were successful in animals.

Indications for and Results of Surgical Treatment of Congenital Cardiopathy, Persistence of the Ductus Arteriosus, and Congenital Stenosis of the Aortic Isthmus. P. Santy. Pédiatrie **11:**19-29 (No. 1) 1956 (In French) [Lyon, France].

Since April, 1948, there have been operated on at the Cardiovascular Surgery Center of Lyon 312 patients with congenital cyanosis, 86 with coarctation of the aortic isthmus, and 78 with patent ductus arteriosus. In the tetralogy of Fallot, the Blalock-Taussig anastomosis was performed 94 times, with a mortality rate of 10.6%, and Potts' anastomosis 124 times, with a mortality rate of 8%. The death rate is higher in patients who do not have the typical tetralogy. Closure of the ductus was performed 78 times, with no deaths. Resection of the stenosed segment of aorta was performed 86 times, with 4 deaths, and the results for the first 60 operations among patients with coarctation were excellent in 29, good in 17, fairly good in 4, and poor in 4. One patient was lost to follow-up. The prognosis is better when operation is performed early.

Postoperative Thyrotoxic Crisis. E. Bezzi. Minerva med. **47:** 386-392 (Feb. 10) 1956 (In Italian) [Turin, Italy].

The author distinguishes between general symptoms of thyrotoxic crisis, especially after surgical intervention on the thyroid or in patients affected by goiter, and classic cases of thyrotoxic crisis. The latter are characterized by an extreme and violent manifestation. Specific preventive therapy is impossible, since the etiology is unknown. It seems that the center of the neurovegetative syndrome is not in the thyroid but rather in a more complex combination of endocrine glands. General sedative therapy of the neurovegetative system has more success than strictly hormonal therapy. The treatment should be similar to that used in shock. Hypothermia (blocking of the neurovegetative system and body cooling) was found very effective by the author. In the treatment of thyrotoxic crisis it is necessary to enable the organism to resist until the general hormonal equilibrium returns spontaneously.

The author studied 47 cases. The use of hypothermia prevented postoperative complications except in two cases where the complications were easy to overcome and one case, which was the only classic case of thyrotoxic crisis. In this case the error was in not continuing the blocking of the neurovegetative system after the body had been cooled. The treatment with hypothermia has an effect on some areas of the pathogenetic mechanism likely to cause a postoperative thyrotoxic crisis, and it also controls the function of the thyroid. The probable post-traumatic reactions are controlled. Hyperthermia, with or without other medical aid, prevents complications such as tachycardia or extrasystoles.

Parathyroid Crisis: Treatment by Emergency Parathyroidectomy. P. R. James and P. G. Richards. A. M. A. Arch. Surg. **72:**553-566 (April) 1956 [Chicago].

The authors add a new case, the 15th, to the 14 cases of acute parathyroid crisis they collected from the literature. The new case concerned a 22-year-old woman. She had been well until 13 months preceding her admission. During this period she was seen by several physicians because of a multitude of complaints, including anorexia, nausea, occasional vomiting, epigastric discomfort, and aching pains in the bones of the lower extremities. She had also noticed polydipsia and polyuria for approximately 10 months. A nodule about 1 to 1.5 cm. in diameter was observed on the inferior aspect of the right lobe of the thyroid.

The history, marked impairment of renal function, nephrolithiasis, and hypercalciuria suggested hyperparathyroidism. Blood chemistry studies revealed hypercalcemia and hypophosphatemia. The patient remained asymptomatic during the first two weeks in the hospital. On the evening of the 15th hospital day, she began to complain of epigastric distress, nausea, and anorexia. During the next 36 hours, the epigastric pain became more severe and was only partially relieved by atropine and meperidine (Demerol) hydrochloride. There developed extreme restlessness, and the pulse was feeble and irregular. She became unresponsive to painful stimuli, moaned constantly, and showed marked restlessness, with continual movement of the arms and legs. Soon thereafter she lapsed into deep coma, showed cyanosis, and had a rectal temperature of 105 F (40.5 C). The close similarity of her clinical picture with that in acute adrenal insufficiency prompted therapeutic measures to combat this possibility. Three hours after the institution of these measures, the blood pressure was faintly audible and the rectal temperature had declined to 100 F (37.8 C). In spite of the continued administration of levarterenol, the blood pressure and pulse were weak and unstable. The serum calcium content was found to be 17 mg. per 100 cc. At the emergency operation the nodule in the right lobe of the thyroid was found to be a solitary adenoma. Further exploration revealed an adenoma of the right superior parathyroid, which was excised. Postoperatively the patient showed gradual improvement.

Chronic hyperparathyroidism may undergo an acute exacerbation. The mechanism producing the acute crisis is poorly understood, but in several reported cases a high calcium-absorbable alkali regimen seemed to have an adverse effect on the disease. In addition, the presence of prolonged immobilization with skeletal demineralization may precipitate an acute crisis. In a suspected case of hyperparathyroidism it would appear advisable to maintain a low calcium intake, avoid undue immobilization, and correct serum electrolyte abnormalities promptly in order to avert dehydration and alkalosis. These factors enhance calcium precipitation in the renal tubules and may lead to acute renal insufficiency. Acute primary hyperparathyroidism, or, more properly, an acute exacerbation or crisis occurring in a chronic primary hyperparathyroidism (due in most cases to a hyperfunctioning parathyroid adenoma), is a surgical emergency necessitating parathyroidectomy.

Treatment of Bleeding from Portal Hypertension in Patients with Cirrhosis of the Liver. C. S. Welch, J. E. Kiley, T. S. Reeve and others. New England J. Med. **254:**493-502 (March 15) 1956 [Boston].

The authors review the clinical records of 50 consecutive patients who had been admitted to the hospital and treated for massive upper gastrointestinal hemorrhage as a result of chronic liver disease and portal hypertension. Hematemesis occurred in 48 of the 50 patients, and in only 2 was the blood passed in the bowel alone. All patients had a large hemorrhage. The presence of varices was definitely established in 45 of the 50 patients by roentgenographic studies, by esophagoscopy, or by postmortem examination. The other five patients were believed to bleed from varices at the gastroesophageal junction. These five patients presented the problem of massive gastrointestinal hemorrhage in the presence of liver disease, probably with portal hypertension. In almost all of the 50 patients with cirrhosis of the liver the diagnosis was made quite readily from the history and physical examination. The laboratory findings were also of some help. A few patients whose disease was proved at autopsy had not undergone any chemical tests, having died of massive hemorrhage soon after admission.

Twenty-eight patients, or slightly over one-half, were treated without any special techniques except general medical care and the replacement of blood, fluids, and electrolytes. These were from the earlier series. Tamponade of the esophagus by use of balloons was used in 19 patients, and 4 patients were operated upon during hemorrhage. Thirty-three, or two-thirds of the pa-

tients, died in the hospital, and 80% of this group died within a year of their hemorrhage. Seventy-six per cent of the patients who had their first hemorrhage died.

Thirty-four per cent of the patients who died after hemorrhage died in coma. Hepatic coma might be initiated by the absorption of large amounts of digested blood in the intestine. The diseased liver cannot metabolize normally the nitrogenous products resulting from the digestion and absorption of the blood in the gastrointestinal tract, so that high values for blood ammonia nitrogen follow hemorrhage from varices in severe cirrhosis. The situation is analogous to the meat-intoxication syndrome that can be induced by meat-feeding in dogs with complete portal-blood diversion into the vena cava.

A three-point program for the treatment of patients with liver disease bleeding from varices can be evolved. Stopping the hemorrhage is the first step, the Sengstaken-Blakemore esophageal balloon tampon being used in addition to blood replacement and treatment of shock. Evacuation of blood from the entire gastrointestinal tract is the second most important step in the treatment. The third therapeutic step consists of reparative and detoxifying measures. The administration of blood, vitamins (especially vitamin K), and concentrated glucose solution are established as useful in improving liver function. The plasma electrolytes must be measured and any deficiencies corrected. Portacaval shunts should be performed in patients with cirrhosis of the liver and esophageal varices before they bleed.

Surgical Experiences in Portal Hypertension: A Review of Nineteen Cases from Brooke Army Hospital. D. G. Fahy, J. F. Schirmer and W. F. Bowers. A. M. A. Arch. Surg. **72**:583-594 (April) 1956 [Chicago].

Data are presented on 19 patients operated on for portal hypertension at Brooke Army Hospital between August, 1952, and July, 1954. Venous shunts between the portal and systemic circulations were constructed in 14 cases. Effective reduction of portal pressure was produced in all but one case, in which thrombosis of the major veins of the portal system precluded the establishment of an adequate shunt. This patient subsequently underwent partial esophagogastrectomy and has had no recurrence of hemorrhage. There were two operative deaths in patients subjected to portacaval shunt. Two other patients died 14 months after shunt, one of liver failure and one of a ruptured cerebral aneurysm. In the 19 patients, counting early and late deaths from all causes and including those in whom only exploration was done, the total case fatality rate was 37%, with 18-to-36-month follow-up.

The only beneficial effect of portacaval shunting operations is reduction of portal venous pressure, and this therapy cannot be expected to be efficacious if the hemorrhage is due to causes other than portal hypertension. An esophageal varix pressure of more than 250 mm. H_2O is a definite indication of portal hypertension, and a patient with this finding should be aided by a shunting procedure. Treatment of esophageal hemorrhage, by means of esophageal vein ligation, esophagogastrectomy, or other operations aimed directly at obliteration of the offending varix should be reserved for those cases in which portal hypertension does not play a part, has been controlled, or is not amenable to correction by portacaval shunting operations or in the occasional case in which hemorrhage cannot be controlled by conservative measures.

Aortic Homograft Substitution for the Postrenal Inferior Vena Cava. L. Blum, W. T. Medl and E. B. C. Keefer. A. M. A. Arch. Surg. **72**:567-570 (April) 1956 [Chicago].

The case described is that of a 29-year-old woman with agenesis of the postrenal portion of the inferior vena cava. Laparotomy revealed that, from the confluence of the common iliac veins, three narrow venules, each 3 mm. in diameter, ran cephalad over the transverse processes of the third, fourth, and fifth lumbar vertebrae to end in a vein of 1.5-cm. diameter that then joined a small oblique right renal vein opposite the second lumbar vertebra. From this junction a vessel corresponding to the inferior vena cava in position, though smaller, continued upward. An aortic bifurcation homograft was inserted, the cephalic anastomosis being located just below the junction with the right renal vein and the caudal anastomoses being made with the external iliac veins 4 cm. above the inguinal ligaments. The left limb of the graft was placed beneath the root of the mesentery and the mesosigmoid. The graft filled promptly after release of the serrefines. One year after the procedure the graft appeared patent by venogram and the patient was symptom-free.

This is the first recorded case in which an aortic bifurcation homograft has been placed in the inferior vena cava. There are reports of two cases in which a segment of aortic homograft has been placed in the superior vena cava. The first of these was a patient with mediastinal malignancy occluding the superior vena cava. The graft was no longer patent four months after the procedure. In the second superior vena cava case, the graft had remained patent 18 months at the time of writing. The problem of substitution in the venous tree is a more difficult one than on the arterial side. The low pressures and sluggish flow of blood increase the hazard of thrombosis. At the present time, even the plastic materials that are of great promise in arterial substitution have been found to be of questionable value in vein replacement. The fact that this patient is doing well one year after placement of the graft suggests that the best available material in situations of this kind is the arterial homograft, whatever its method of preservation.

Bronchogenic Carcinoma in Persons Under Forty Years of Age. H. W. Neuman, F. H. Ellis Jr. and J. R. McDonald. New England J. Med. **254**:502-507 (March 15) 1956 [Boston].

The records of patients under 40 years of age in whom the diagnosis of primary bronchogenic carcinoma had been made at the Mayo Clinic in the years 1943 through 1954 were reviewed. There was a total of 51 patients, 39 men and 12 women. The ratio of men to women (3.25:1) was appreciably lower than that reported for bronchogenic carcinoma in all ages, which varies from 5:1 to 10:1. Two patients were entirely asymptomatic. In the remaining 49 the duration of symptoms, before the diagnosis was established, varied from two weeks to 12 months, the average being 4.3 months. Forty-three patients had symptoms referable to the respiratory tract. The most frequent were cough and hemoptysis. Twelve had symptoms referable to distant metastasis, and 11 had symptoms referable to involvement by direct extension of structures adjacent to the primary lesion. On the basis of symptoms alone, however, 16 patients (31%) gave evidence of inoperability by reason of distant or local spread. Bronchoscopy was carried out in 32 patients, and in 21 the diagnosis was established by bronchoscopic visualization and biopsy of the lesion. In 10 patients the diagnosis of primary bronchogenic carcinoma was made on the basis of clinical and roentgenographic findings and on histological examination of tissue removed at biopsy from distant metastatic foci. In nine patients the diagnosis was proved by the findings of malignant cells on cytological examination of sputum or bronchial secretions; in eight the diagnosis was established at surgical exploration of the thorax. In the remaining three the diagnosis was proved at autopsy.

The lesions were considered inoperable in 32 (63%) of the 51 patients. The remaining 19 patients were considered to have operable lesions and were subjected to thoracotomy. Resection with a view to cure was possible in nine patients, giving a rate of curative resection of 17.7% of the entire 51 cases. Resection with a view to palliation was possible in four. The lesions were nonresectable in six patients. Of the nine patients who underwent curative pneumonectomy, one is living and is apparently well three and a half years after operation. Of the remaining eight patients, 7 died within 5 to 13 months of operation and one, who died four years after operation, was shown at autopsy to have died of bronchogenic carcinoma. Bronchogenic carcinoma is more rapidly fatal in patients under 40 years of age than in older persons. The chances of cure or even long survival are small and are practically nonexistent when metastasis to hilar lymph nodes has occurred. With the possible exception of squamous-cell lesions, which are infrequent in males and rare in females under 40 years of age, the cell type does not appear to have prognostic significance in bronchogenic carcinoma in this age group.

NEUROLOGY & PSYCHIATRY

Surgery in Spontaneous Subarachnoid Hemorrhage: Operative Treatment of Aneurysms on the Anterior Cerebral and Anterior Communicating Artery. V. Logue. Brit. M. J. 1:473-479 (March 3) 1956 [London, England].

Seventy-three patients were admitted to the neurosurgical departments of two hospitals in London, England, with ruptured aneurysms situated on and about the anterior communicating artery and its junction with the anterior cerebral arteries. Thirty-seven of these, between the ages of 23 and 62 years, underwent surgical treatment, while 36 patients who were treated conservatively by the usual methods with bed rest for six weeks as the essential feature served as controls. The operative procedure consisted of occlusion by a clip of the anterior cerebral artery responsible for the filling of the aneurysmal sac as judged by arteriography. Of the 36 patients treated conservatively, 16 died, a mortality rate of 44.4%, and 20 survived, 4 (20%) of whom had a severe and persistent neurological disability. Of the 37 patients, 17 were operated on within seven days after the hemorrhage and 5 of these died, an operative mortality of 13.5%. Of the six patients operated on within 24 hours of the hemorrhage, two died. Of the 20 patients operated on after the first week, all survived. Thus the time interval from hemorrhage to surgical intervention is the all-important factor. Surgery should not be performed when the patient is still in coma, but in order to prevent further hemorrhage it should be done as soon as the spasm of the vessels in continuity with the aneurysm and for a varying distance around it has passed off. In only one (3%) of the 32 survivors did a fatal recurrent hemorrhage occur, on the eighth postoperative day, and one patient died of pulmonary embolism three and a half months after the operation. There were three instances of ischemic or thrombotic damage after the operation in the 30 surviving patients, an incidence of 10%. Of these 30 patients, 24 were leading reasonably full working lives, while 6 were incapable of working; 3 of these had permanent severe intellectual and/or physical disability, a morbidity rate of 10%. Although the operation performed by the author is not the final answer to the treatment of anterior cerebral aneurysms, it has a good deal to offer to the patient under the age of 60 years in the acute phase of aneurysmal hemorrhage.

Use of ACTH and Cortisone Combined with Antibiotic and Chemotherapeutic Preparations in Treatment of Tuberculous Meningitis. G. Conese and L. Colonna. Policlinico (sez. med.) 63:38-50 (Jan.-Feb.) 1956 (In Italian) [Rome, Italy].

Good results are reported in nine adult patients with tuberculous meningitis who were treated with streptomycin, aminosalicylic acid, isoniazid, and corticotropin and cortisone. Some of the patients were in extremely poor general condition, with high fever, vomiting, and signs of meningeal irritation. Others had only low fever, inconstant headache, mental lethargy, and slight meningeal involvement. The patients were given daily 1 gm. of streptomycin intramuscularly and 10 gm. of aminosalicylic acid and 200 mg. of isoniazid orally. The hormones were given separately (corticotropin in daily doses of 12 mg. intradermally and cortisone in daily doses of 100 mg. intramuscularly) or in combination. In some instances their administration was begun on the first days of the illness, in others only after the antibiotic therapy had greatly improved the clinical symptoms but had left unchanged the cerebrospinal fluid findings. Results were excellent in six patients in whom the clinical and cerebrospinal findings were restored to normal. In the other three, the clinical findings returned to normal whereas the cerebrospinal picture remained altered. However, one of these had a positive reaction for syphilis and the other two did not continue, after they had been discharged, the suggested antisyphilitic therapy.

In all the patients the general and cerebromeningeal clinical symptoms were influenced by the therapy sooner than the spinal fluid alterations. No toxic phenomenon was observed during the therapy, and the high temperature dropped in from two to four weeks. The only complication that was seen after at least one month of the hormone therapy was the appearance of moon-face, and this despite the fact that a low-salt diet and diuretic preparations were given. A follow-up of the patients 2 to 12 months after the therapy showed relapses in the three patients mentioned earlier. As to the best time for interruption of the hormone therapy, the authors state that it depends on the findings in the cerebrospinal fluid. They continued it for about 10 days after the findings had improved, whereas the antibiotic therapy was continued for several months thereafter. With regard to the mechanism of action of these hormones, it may be that by inhibiting the local defense reactivity they prevent the formation of the fibrotic tissue that is responsible for the severe sequelae of meningitis. Also, the fact that they prevent the formation of a block could lead to a better penetration and, therefore, a greater therapeutic action of the antibiotics. Whatever the mechanism of these hormones, the results obtained in these patients were better than those that result from the administration of antibiotic and chemotherapeutic preparations alone.

Treatment of the Convulsive State by Barbiturate Infiltration of the Brain. F. Jelasic. Presse méd. 64:375-376 (Feb. 29) 1956 (In French) [Paris, France].

The present report comes from the General Hospital of Pula, Yugoslavia. The convulsive state has a poor prognosis. Anticonvulsants reaching the brain via the blood stream affect not only the epileptic focus but also other portions. Large doses of them are necessary to calm the pathological activity of the brain, and these will also block the subcortical centers and deepen coma. The inhibitory effect of barbiturates injected directly into the diseased brain was demonstrated in dogs in which the electrical excitability of the infiltrated hemisphere was shown to be diminished. In a patient with intractable convulsions consequent to cranial injury, barbiturate (Hexobarbitone) infiltration of the hemorrhagic portion stopped the epileptic attacks. Two weeks later he was discharged from hospital with no neurological symptoms. Another patient, who had numerous generalized attacks, was greatly benefited by this treatment. Her lesions were too extensive to permit excision. The method of administration in this instance was from 0.1 to 0.2 gm. of Hexobarbitone spread over three sites. This was repeated three times in a period of 20 days. One of the injections given in the parietal region caused paralysis of the left hand and foot lasting five minutes. It was assumed that the pyramidal fascia had been infiltrated also, owing to the deep position of the needle. Direct intracerebral application of anticonvulsive drugs thus appears to be valuable, but its precise value can be assessed only after clinical trials on a larger scale.

Successive Observations on the Therapy of Tuberculous Meningitis. N. Sanguigno and A. Carini. Policlinico (sez. prat.) 63: 245-254 (Feb. 20) 1956 (In Italian) [Rome, Italy].

The authors compare the results they achieved in a previous group of 32 patients with tuberculous meningitis treated with streptomycin or with streptomycin and PAS with those in a second group of 21 patients treated with streptomycin and isoniazid. The mortality in the first group was 90.6%, and among the 9.4% who did not die the consequences of the disease were severe. In the 21 patients in the second group, treatment with streptomycin and isoniazid resulted in 20 cures (95.2%), with one patient still under treatment. Serious sequelae resulted in six cases only. Isoniazid was given mainly by the oral route, and only in special cases were intraspinal injections used. The treatment lasted from a minimum of two months to a maximum of one year. The authors noticed that the earlier the treatment was started, the better the results. Among the other advantages of treatment with isoniazid is the fact that the restoration of nitrogen balance is much more rapid than with treatments previously used.

The addition of isoniazid to streptomycin has given results that have rendered obsolete those obtained with streptomycin alone or in association with PAS. In order to avoid the side-effects resulting from the use of streptomycin, it would seem advisable to use only isoniazid in the treatment of meningitis. But these authors feel that a complete elimination of streptomycin would be dangerous. The positive therapeutic effect of this drug on meningitis makes it an essential in the treatment. The authors believe that it is not even possible to do away with intraspinal injections of streptomycin. At most, the doses may be decreased. Isoniazid is more effectively administered by

the oral route than is streptomycin. Now that a successful treatment with isoniazid and streptomycin has been developed, PAS assumes only a complementary role in the treatment of tuberculous meningitis. The obstacle presented at one time by the age of the patient has been surmounted with the use of isoniazid. The problem of serious sequelae is the only one that still prevents the authors from considering treatment with streptomycin and isoniazid as the ideal therapy in cases of tuberculous meningitis.

Neuritis Associated with Systemic Lupus Erythematosus. A. A. Bailey, G. P. Sayre and E. C. Clark. A. M. A. Arch. Neurol. & Psychiat. **75**:251-259 (March) 1956 [Chicago].

Since 1949, five patients with systemic lupus erythematosus and associated neuritic involvement have been examined clinically at the Mayo Clinic. The patients had variable manifestations of neuritis, in addition to the typical signs and symptoms of systemic lupus erythematosus. There was in all cases a history of migrating arthralgias, fever, weakness, and malaise. Though not considered necessary for the diagnosis of lupus erythematosus, the erythematous rash over the nose and cheeks was present in several cases. Leukopenia, elevation of the sedimentation rate, false-positive blood serologic reactions for syphilis, thrombocytopenia, L. E. cells in sternal aspiration material, and positive results of L. E. clot tests were found in some or all of the patients. In addition to the neuritis, four of the five patients had other signs of involvement of the nervous system, such as diplopia, nystagmus, confusion, anxiety, and convulsions.

Examination of the first two patients revealed findings suggestive of the syndrome of infective neuronitis (Guillain-Barré syndrome). In the third patient and to some extent in the fourth, the neuritis seemed to be peripheral in type. Other findings in the fourth and those in the fifth patient suggested involvement of the mononeuritis multiplex type. Autopsy was done in two of the patients. It revealed focal degeneration of the peripheral nerves and posterior ganglia and secondary degeneration of the posterior columns. In one case, no associated cause for this degeneration was noted; in the other, lesions of periarteritis of the blood vessels of the peripheral nerves and elsewhere were present. As this patient received cortisone, it is of interest to note that Slocumb has reported the appearance of periarteritis nodosa in rheumatic patients on withdrawal of cortisone. However, it cannot be said that cortisone was necessarily related to the arteritis, since vascular changes have been noted in lupus erythematosus before the cortisone era.

Traumatic Intracerebral Hematoma: Review of 16 Surgically Treated Cases. R. L. McLaurin and B. H. McBride. Ann. Surg. **143**:294-305 (March) 1956 [Philadelphia].

Clinical histories, operative findings, and end-results in 16 patients between the ages of 9 and 65 years with traumatic intracerebral hematoma treated at the division of neurosurgery of the University of Cincinnati, Ohio, are reviewed. The injuries were sustained by either sudden acceleration or sudden deceleration of the head; thus, all injuries to the intracranial contents were of the coup-contrecoup variety. There is no characteristic clinical syndrome indicating the presence of intracranial hemorrhage. The sequence of coma, lucid interval, and progressive deterioration of conscious level with or without hemiplegia, which was observed in many of these patients, is pathognomonic simply of an intracranial hematoma in any location. The following plan of procedure is presented: Exploratory bur holes are routinely placed in the temporal and parieto-occipital areas bilaterally. The temporal openings are enlarged to allow adequate visualization of the temporal cortex and to eliminate a hematoma beneath the temporal lobe. If a surface hematoma is observed, it is evacuated. Further investigation is required if no surface hematoma is found, if the hematoma is of insufficient magnitude to account for the clinical aspect, or if, after the removal of the hematoma, the brain herniates through the dural opening. If no surface hematoma is visible and if the patient's condition is critical, needling of the temporal lobe is justified. Although aspiration is probably ineffective in completely removing a hematoma, especially during the first few days, abnormal consistency of the brain substance may be felt. Under such circumstances a transcortical incision is advised to allow visualization and complete removal of the blood clot and surrounding necrotic tissue.

If the patient's condition is not critical after surface exploration, contrast roentgenographic studies are indicated to determine the presence and exact location of an intracerebral hematoma. The posterior trephine holes having already been placed, the patient is ready for air injection without delay. Ventriculography is probably preferable to angiography because of more complete visualization of the intracranial contents. If contrast studies confirm the presence of a space-taking lesion, craniotomy and complete evacuation under direct vision are necessary. Of the 16 patients, 12 had a temporal hematoma, 3 a frontal hematoma, and only one had a parieto-occipital hematoma. Since hematomas after trauma are almost invariably located within the anterior temporal and prefrontal lobes, the hazard of increasing neurological deficit by cortical incision does not exist.

Two of the 16 patients died. One of the two was neurologically asymptomatic until his death, which occurred from tuberculosis five years after the removal of the hematoma. The second patient was the only one who died as a result of the injury, six weeks after the removal of a right temporal lobe hematoma; autopsy revealed that a subdural hematoma in the parietal region had apparently been missed at the operation. Of the remaining 14 patients who were followed up for periods varying from two months to six years, 9 were completely asymptomatic and the others showed a minimal degree of neurological deficit. The end-results of surgical evacuation thus justify many negative explorations. The prognosis in severe craniocerebral trauma appears to be better for complete recovery from effects of intracerebral hemorrhage than from similar effects caused by meningeal hemorrhage or cerebral contusion.

Intracranial Tuberculomas: A Review of Clinical Features and Treatment. W. A. Sibley and J. L. O'Brien. Neurology **6**:157-165 (March) 1956 [Minneapolis].

A review of the clinical and pathological records at the Columbia-Presbyterian Medical Center in New York between 1933 and 1955 revealed that 18 patients had microscopically verified tuberculomas of the brain with symptoms and signs of intracranial tumor during life. Seizures and increased intracranial pressure were present in most of these patients and made diagnosis difficult before surgical intervention or autopsy. The true nature of the tumor was diagnosed before the operation in only one of these patients. Eight patients received antituberculous drug therapy in the postoperative period. An additional 94 patients with intracranial tuberculoma, whose cases were collected from the literature after 1947, were operated on and received an antituberculous drug. Of the total of 102 patients, 23 died, but only 5 of these deaths were attributed to meningitis, although this complication occurred in 7 patients in the postoperative period. Fifteen deaths resulted from the operation itself. The over-all mortality rate of about 22% represents a striking improvement in results since the introduction of specific therapy.

The development of tuberculous meningitis in the postoperative period was prevented in most patients by the daily administration of streptomycin continued for 60 to 90 days after the operation. Treatment for longer periods of time, in the absence of meningitis or extracranial tuberculosis, probably has no definite advantages and would enhance the risk of drug toxicity and development of bacteriological resistance. Isoniazid and aminosalicylic acid should be used in addition to streptomycin, although few patients so treated have been reported on as yet and the optimum duration of therapy with these drugs cannot be stated. Frequent analyses of the spinal fluid should be performed for several months postoperatively. Evidence of meningitis requires more prolonged therapy in accordance with modern concepts of the treatment of that disease.

Observations on the Pain and Trigger Mechanism in Trigeminal Neuralgia. B. L. Crue, C. H. Shelden, R. H. Pudenz and D. B. Freshwater. Neurology **6**:196-207 (March) 1956 [Minneapolis].

Ten patients with intense pain in the distribution of the third or second division of the trigeminal nerve were treated by the authors with a decompression procedure carried out at the foramen rotundum or foramen ovale with neurolysis of the involved

nerve. The immediate results were good. There was cessation of pain, with only a minimal hypalgesia and no operative morbidity. Five patients had a recurrence of the symptoms. The other five have remained free of recurrence for from two to four years. During the same period Taarnhøj of Copenhagen, Denmark, obtained similar results in his patients with trigeminal neuralgia by decompressing the posterior root. If relief of pain in trigeminal neuralgia could be obtained by decompression of either the posterior root or the peripheral branches, the two methods must have something in common. It was considered that the trauma of surgery rather than the decompression may have been the curative factor in both of the so-called decompression procedures.

The authors decided to try merely compressing the trigeminal nerve, and this was done with a retrogasserian approach in 28 patients. An attempt was made to compress selectively only those fibers coming from the division involved. Results were most gratifying. There has been no failure of pain relief and no surgical morbidity. At the time of writing, there was no recurrence up to 15 months. The good results obtained by Wyburn-Mason in England in his patients with trigeminal neuralgia, who were subjected to alcohol block or section of the greater auricular nerve, induced the authors to perform lidocaine (Xylocaine) hydrochloride block on 30 patients with trigeminal pain in various combinations in all three divisions. Eleven patients obtained complete or almost complete relief from tic pain, and surgical section or crushing of the greater auricular nerve was done. This proved adequate in five patients, but six others had a recurrence, and in five of these a trigeminal compression was done. The results of trigeminal compression and those of initial greater auricular nerve section suggested that the interruption of sensory stimuli into the central connections of the upper cervical cord might in some way play a role in the cessation of tic pain. An attempt was made to try blocks of the occipital nerve as well as of the greater auricular nerve. Results suggested that, if a block of one nerve does not completely relieve the pain, blocking the other nerve will sometimes add to the effect regardless of the division in which the pain is centered. There seems to be a relationship between the division in which the pain or trigger is located and the nerve blocked. If anesthesia is produced in the contiguous or overlapping area, the results seem to be better. Thus the authors usually block the greater auricular and, at times, the lesser occipital and cutaneous colli branches for third division pain and the occipital for first division pain or trigger.

If blocking the higher cervical nerves can stop the pain even in a few cases, there must be a connection in the pain mechanism. Regardless of the original cause, the preponderance of evidence seems to indicate some central type of mechanism in trigeminal pain, most probably in the upper cervical cord where the descending sensory nucleus of the fifth cranial nerve must be in juxtaposition with the incoming upper cervical sensory fibers. The authors consider trigeminal compression as the standard surgical procedure for trigeminal neuralgia. It is of particular value in bilateral disease. Perhaps no patient should be subjected to craniotomy until the simple procedure of local cervical nerve block has been tried.

Cranial Dyssynosteosis, Especially Tower Skull: Its Symptoms and Etiology. T. I. Bertelsen. Nord. med. **55**:147-150 (Feb. 2) 1956 (In Danish) [Stockholm, Sweden].

Of 150 patients with cranial dyssynosteosis seen in the neurosurgical departments in Copenhagen and Århus and the Institute for the Blind in Copenhagen, 117 had oxycephaly (tower skull), including hypertelorism (Crouzon's disease) and acrocephalosyndactylia (Apert's disease), 14 had scaphocephalism, and the rest had various other forms. Symptoms seem to appear especially in early childhood and after growth is ended. The gravest symptoms are in the oxycephalic group. Twenty-one of the 100 oxycephalic patients from the neurological departments were psychically retarded. The low stature often seen in oxycephalic patients is attributed to reduced hypophysis function. Heredity seems to play no part except in Crouzon's and Apert's diseases. The impaired vision associated with oxycephaly occurs in childhood in connection with increased cranial pressure. In children, papillary stasis with succeeding atrophy of the optic nerve is the gravest symptom; in adults the dominating symptoms are headache and convulsions, probably sequels of brain atrophy. Early decompression operation, now most often performed as a linear craniotomy along the sutures ossified too early, will in some cases save vision in a child with papillary stasis due to oxycephaly. Because of the frequent occurrence of twins in the case material, intrauterine conditions, perhaps particularly space conditions in the uterus, are believed to be significant. Blindness due to oxycephaly has become less frequent in recent years, and the disease itself is thought to be less common as the result of the improved hygiene of pregnancy.

Complications of Meningococcus Infection in a Series of Sixty-Three Consecutive Sporadic Cases. J. L. Tobin. Am. J. M. Sc. **231**:241-248 (March) 1956 [Philadelphia].

Sixty-three sporadic cases of meningococcic meningitis occurred during a four-year period at an Air Force recruit training base with a constantly changing population of 15,000 recruits. There was never more than one case in the same flight (a group of 72 men who work together and live in the same barracks), presumably because 2 gm. of sulfadiazine was given as a preventive measure to each member of the flight in which a case of meningitis developed as soon as the diagnosis was made. The disease occurred under conditions allowing early discovery, and treatment with sulfadiazine and penicillin was begun at once. In spite of early treatment, complications developed in 32, that is, in more than half of the 63 patients. The most serious complication was the Waterhouse-Friderichsen syndrome (fulminating meningococcic meningitis), which accounted for four of the six deaths that occurred in this series. There were nine patients who had the characteristics of the Waterhouse-Friderichsen syndrome, which are extensive coalescing petechiae, ecchymotic areas, and peripheral vascular collapse. Most of these patients arrived at the hospital in shock.

Although the best results were expected from cortisone, its effects were not spectacular. Continuous intravenous administration of norepinephrine usually raised the blood pressure but did not necessarily sustain it. Perhaps the adrenal had already been damaged to such an extent that the rate of absorption of even intramuscularly administered cortisone could not mend it. For this reason, the author expected better results from intravenous administration. However, one of the patients, in whom this medicament was used when his blood pressure took a sudden drop, failed to recover. At present the authors administer cortisone as soon as the diagnosis is established. Autopsies in the four patients who died from the Waterhouse-Friderichsen syndrome revealed extensive bilateral adrenal hemorrhage in three and congestion of the adrenals in the fourth.

Severe gastrointestinal hemorrhage occurred in two of the patients. In one of these it occurred on the seventh day and was the immediate cause of death. The site of bleeding was superficial ulceration in the prepyloric region of the stomach. In the other it occurred at the end of the second day and was manifested by the passage of a copious tarry stool. At autopsy, no particular source of bleeding was discovered. Acute pulmonary edema developed in one of the patients, in whom autopsy revealed a small area of hemorrhage in one of the adrenals. Neurological complications, which developed in 17 patients, included eye muscle paresis, hearing loss, herpes zoster, sensory loss, and facial paralysis. In all patients with extensive rashes, superficial gangrenous areas that break down into ulcers are likely to develop. The greatest difficulty occurs in patients with the Waterhouse-Friderichsen syndrome; of the nine skin complications, five were associated with this syndrome. Electrocardiographic changes occurred in six patients.

Antigenicity Studies on Salk-Type Poliomyelitis Vaccine. D. Tyrell, S. A. Keeble and W. Wood. Brit. M. J. **1**:598-601 (March 17) 1956 [London, England].

Serum antibody titers were determined in mice, monkeys, and in 15 human volunteers after administration of a Salk-type trivalent poliomyelitis vaccine prepared in Britain from type 1, 2, and 3 poliomyelitis viruses. Despite the small number of persons subjected to tests, there appeared a broad measure of correlation between the serum antibody titers detected in

monkeys and in persons of group A, that is, persons with no antibody to any virus type before inoculation with the vaccine. This correlation was also shown when the separate responses to each of the three types of antigens were considered. As a guide, therefore, to the probable effectiveness of a batch of vaccine in man, it seems that the monkey is a satisfactory laboratory animal. The antibody response in mice appears to be a less sensitive measure of vaccine potency. The results of the challenge test in mice, however, in which 45% of mice that had received undiluted vaccine survived an intracerebral inoculation with living type 2 virus, indicate that the presence of only moderate serum antibody titers is associated with significant active immunity. It might be expected, therefore, that similar antibody levels in man would result in an even greater degree of protection, since in natural infections the virus reaches the central nervous system indirectly, after a stage of multiplication in the alimentary tract, rather than being introduced directly into the brain. The serological responses of the men to whom this poliomyelitis vaccine was administered, i. e., the marked rise in antibody titers against each virus component of the vaccine after the first injection of the vaccine, justify the conclusion that the vaccine is an effective antigen for adult humans, although there is some suggestion that the type 3 component in this particular batch was not so potent as the type 1 and type 2 components.

GYNECOLOGY & OBSTETRICS

Diamox, a Carbonic Anhydrase Inhibitor, as an Oral Diuretic in Pregnancy. J. R. Ashe Jr., B. Carter, W. L. Thomas and W. R. Kerr. Obst. & Gynec. 7:242-248 (March) 1956 [New York].

Acetazolamide (Diamox) was given orally to 100 pregnant women, 49 of whom had preeclampsia, 3 hypertensive vascular disease, 7 hypertensive vascular disease with superimposed preeclampsia, 3 hypertensive cardiovascular disease with superimposed preeclampsia, 2 edema with excessive weight gain, and 36 excessive weight gain. Acetazolamide was administered in doses of 250 mg. every morning for five days, followed by two days of rest from the drug. This regimen should be continued until delivery. Of the 100 pregnant women, 67 showed a good response, with blood pressure restored to normal, weight loss, and disappearance of edema and albuminuria; 24 showed an average response, with lowering of blood pressure, weight loss, and decrease in edema and in albuminuria; and 9 showed a poor response. In 32 patients with mild preeclampsia, there was a reversal of the disease and a dramatic readjustment of the patient's renal and vascular status with disappearance of all signs and symptoms of preeclampsia. In 20 patients with excessive weight gain who showed an adequate response to the drug, weight gain and/or edema returned when administration of the drug was discontinued. Preeclampsia developed in four of these patients. This indicates the necessity for the continued administration of the drug even though an adequate clinical response has occurred. The fetal mortality rate was 3.06%. No severe side-effects in mother or infant were noted.

Acetazolamide inhibits carbonic anhydrase activity with a resulting decrease in the production of hydrogen ions in the renal tubular cells. When hydrogen-ion concentration is decreased, the excretion of potassium ions, which compete with hydrogen ions for excretion in the renal tubules, becomes uninhibited. Thus there occurs a copious diuresis of sodium, potassium, bicarbonate radical, and water in the 6-to-12-hour period after the administration of the drug. Acetazolamide as an effective diuretic is useful in the management of toxemia, edema, and excessive weight gain caused by water retention in pregnancy.

Measurements of Aldosterone in the Eclamptogenic Toxemias of Pregnancy. A. C. Barnes and E. J. Quilligan. Am. J. Obst. & Gynec. 71:670-682 (March) 1956 [St. Louis].

Aldosterone has the most vigorous sodium-retaining action of any of the steroids yet identified. This steroid has been detected in the urine of patients with heart failure, nephrosis, cirrhosis of the liver, preeclampsia, and eclampsia. Women with the eclamptogenic toxemias demonstrate a marked increase in the sodium-retaining activity of the urinary corticoids, but some nontoxemic pregnant patients also demonstrate increased excretion of this factor, while some individual toxemic women show no such change. Diuresis diminished the amount found, although in all other respects the patient's clinical picture may have remained the same. By the technique of measurement used by the authors, it had disappeared from the urine after the third postpartum day in all cases. Placental extracts did not contain a strong sodium-retaining fraction. Chromatographic quantitations of aldosterone indicated in normal pregnant women a higher range than that reported for the nonpregnant. Attempts to increase this factor by the administration of steroids were unsuccessful. The results with prolonged administration of corticotropin in a small group of women were not conclusive, but cannot be called negative. The pregnant woman in the last trimester responds to sodium restriction with some increase in the urinary aldosterone. Adding a potassium load has not demonstrably increased the excretion of the sodium-retaining factor, aldosterone.

This steroid has not been demonstrated to be the cause of the edema in the eclamptogenic toxemias, and it could be a sequel as much as a cause of the syndrome. It forms a part of the normal mechanism for electrolyte control, and its role as an eliminator of potassium will require additional study of the metabolism of this ion in toxemia. Aldosterone causes not only sodium retention but also the elimination of potassium. The latter function is obviously of greater importance in human homeostasis. An elevation of blood potassium is fatal; indeed, the principal function of the artificial kidney is to lower the potassium level rather than the level of nitrogenous waste products. Under these circumstances it is almost inconceivable that there should not be a protective mechanism that can be triggered to eliminate excess potassium. If such a mechanism had the coincidental tendency to retain sodium, or if the patient were particularly susceptible to sodium retention, the accumulation of salt and water might well be a by-product of the need to eliminate potassium.

Placental Tumors: Hemangiomas, with Special Reference to an Associated Clinical Syndrome. E. J. DeCosta, A. B. Gerbie, R. H. Andresen and T. C. Gallanis. Obst. & Gynec. 7:249-259 (March) 1956 [New York].

Two hundred fifty-two cases of hemangioma of the placenta were collected from the literature; one-third of the patients with placental hemangiomas had a typical syndrome characterized by hydramnios and prematurity. In addition, perinatal fetal loss and the incidence of both antepartum and postpartum hemorrhage was higher than normal. Five additional patients with hemangiomas of the placenta are reported on by the authors. Two of these patients were asymptomatic and three had the typical syndrome. Large hemangiomas (liver and extremities) occurred in three of the infants delivered by these patients. This observation indicates that there may be a genetic predisposition to the development of vascular tumors.

Benign tumors of the placenta are usually hemangiomas. They occur infrequently but have sufficient clinical importance to warrant consideration. Despite repeated references in the literature, the standard textbooks fail to mention the clinical significance of hemangiomas of the placenta. Pathological examination revealed that, although these tumors are usually observed as an elevation of the fetal surface of the placenta, they also may be seen on the maternal surface or occasionally attached to the cord. Marchetti classified these tumors microscopically according to the ratio of vascular tissue to connective tissue and described three types as follows: (1) a vascular or mature form characterized by numerous small blood vessels supported by a loose network of chorionic stromal cells; (2) a cellular or less mature form, which is compact, consisting of an abundance of endothelial and stromal cells; and (3) a form displaying various degrees of degeneration. Microscopic examination of the tumors in the authors' patients showed all three histological variations described by Marchetti.

Experience with Radioactive Colloidal Gold in the Treatment of Ovarian Carcinoma. W. C. Keettel and H. B. Elkins. Am. J. Obst. & Gynec. **71**:553-568 (March) 1956 [St. Louis].

A cytological study of peritoneal washings in patients with ovarian malignancy was initiated to determine if abnormal cells could be detected in the fluid removed from the peritoneal cavity or the cul-de-sac. The first part of the paper is concerned with the results of the cytological studies; the second part describes the present management of ovarian carcinoma and summarizes experiences with radioactive colloidal gold therapy. In 247 patients, cul-de-sac aspirations at the time of dilation and curettage revealed no abnormal cells. In 275 patients, peritoneal washings at laparotomy revealed abnormal cells in 17 instances. Fourteen of these women had ovarian cancer, two had extensive uterine malignancy, and in one instance the peritoneal washings gave a false-positive reaction. Five patients with cystadenocarcinoma showed no clinical evidence of spread, although abnormal cells were found in the peritoneal washings. Patients with stage 1 and 2A ovarian carcinoma are now treated with abdominal total hysterectomy, bilateral salpingo-oophorectomy, and radioactive gold, Au^{198}. The remainder of the patients with ovarian carcinoma are treated with surgery, external irradiation, and radioactive gold when feasible. The majority of patients tolerate Au^{198} with minimal complications. Colloidal gold is of value in controlling formation of ascitic fluid in certain patients. Sufficient time has not elapsed to evaluate five-year survival rates; but results seem encouraging.

PEDIATRICS

Studies in Rheumatic Fever: 1. Nutrition as a Factor Conditioning the Incidence and Course of Rheumatic Fever; 2. Experience Since the Advent of Corticotropin and Cortisone; 3. Effect of Activity and Rest on Nutritional State in Rheumatic Fever. J. A. Johnston. A. M. A. J. Dis. Child. **91**:250-267 (March) 1956 [Chicago].

Of 214 children with rheumatic fever whose dietary histories were analyzed in regard to the outcome in rheumatic fever, 148 had been on an adequate diet and 66 on an inadequate diet. Among the 148, the outcome of the disease was satisfactory in 131 and unsatisfactory in 17, while among the 66 the outcome was satisfactory in 52 and unsatisfactory in 14. These data, although not highly significant, suggest that the outcome in rheumatic fever is influenced by the nutritional state. By using the Wetzel grid to classify the nutritional state of 230 children with rheumatic fever and by comparing their standing on the Wetzel grid with the outcome in rheumatic fever, a high correlation was found between a favorable outcome and an advantageous channel on the Wetzel grid. Metabolic balance studies for nitrogen and calcium carried out in 30 children with rheumatic fever revealed the existence of deficits in nitrogen and calcium as judged by the high retention of these substances with flat or declining weight curves. Prolonged bed rest influenced adversely the retention of nitrogen and calcium; very moderate degrees of activity offset this.

The outcome of rheumatic fever in 76 children treated with cortisone or corticotropin combined with salicylates and ascorbic acid was compared with that of 270 children who had been treated before the advent of the hormones. The outcome in rheumatic fever was significantly better in those on the combined regimen than in those on previous regimens, though this statement must be qualified by recognition of the fact that there has been a decline in the severity of the disease in the past 10 years. In the management of the child with rheumatic fever, consideration should be given to all the factors that influence nutrition, as judged by the retention of nitrogen and calcium, the dietary intake, focal infection, hormones, rest, and activity.

Results of Cortisone and ACTH Treatment of Rheumatic Fever. M. S. Hecht, W. E. Shelden, A. Nolke and others. J. Pediat. **48**:300-307 (March) 1956 [St. Louis].

Hecht and associates report on results obtained with cortisone and corticotropin in patients with active rheumatic fever and carditis admitted to the Children's Hospital of Michigan between April, 1950, when the authors started this form of treatment, and September, 1953. There was at least one year of follow-up for every patient. The cases presented in an earlier report are included in this study. The authors also reviewed the records of the patients with rheumatic fever admitted to their hospital from December, 1946, to April, 1950, and compare the results obtained during that period, when salicylates, chiefly aspirin, were used, with results in the hormone-treated patients in respect to the disappearance of valve lesions and the number of deaths. Patients were 12 years of age or less when treatment was begun. There were 122 hormone-treated patients under observation during treatment and convalescence. They have been followed up for at least one year, and the majority are still under observation.

The initial group of 44 patients was about equally divided between those receiving corticotropin and those on cortisone therapy, but in the more recent cases the authors resorted mostly to oral therapy with cortisone, giving it at 6-hour intervals. They commenced with a daily dose of 300 mg.; from the third to the seventh day they gave 200 mg., then 150 mg. for two weeks, 100 mg. for three weeks, 75 mg. for four days, and 50 mg. for three days. Recently they have maintained the 150-mg. level for longer and the 100-mg. level for shorter periods. In most cases 150 mg. per day will keep rheumatic activity apparently suppressed. Small children may need only 100 mg. They found it impossible to give enough cortisone or corticotropin to suppress rheumatic activity without producing some signs of adrenal cortical hyperfunction (Cushing's syndrome). They disregard moon face, obesity, and hirsutism. These usually disappeared later. The number of deaths in the hormone-treated group was less than that in the earlier salicylate-treated group. The incidence of reversal of signs of valvular lesions in first attacks of hormone-treated patients has been greater than in the prehormone period. Cortisone does not cure rheumatic fever. The authors use it to lessen the damage from the attack. In some patients, rheumatic fever pursues a low-grade course of long duration. In such cases, long-term use of the hormones might do more harm than good. In subacute as well as in acute rheumatic fever, if proper precautions are taken, the dangers in the use of cortisone and corticotropin are not great in relation to the seriousness of the disease. The administration of these hormones does not interfere with natural recovery from attacks of rheumatic fever. Whether or not the total duration of individual attacks is changed is extremely difficult to prove because of the variability of the disease, the chronicity of many cases, and the indefinite endpoint of low-grade activity.

Meconium Ileus: A Clinical Study of 20 Surviving Patients. H. Shwachman, C. V. Pryles and R. E. Gross. A. M. A. J. Dis. Child. **91**:223-244 (March) 1956 [Chicago].

The authors studied 20 infants with meconium ileus born between October, 1941, and January, 1955, who survived. These patients were followed up to July, 1955. The intestinal obstruction was successfully relieved by Mikulicz resection with a double-barrel ileoileostomy in 15 and by conservative medical treatment in 5 who had meconium obstruction of mild degree and who later showed evidence of pancreatic insufficiency. Despite early institution of antibiotic therapy, pulmonary symptoms and signs appeared in the course of the first few months of life in 13 surgically treated patients and in four patients who were treated conservatively. Roentgenographic examination of the lungs revealed uniform changes varying only in degree of involvement. These changes consisted of irregular aeration, increased bronchovascular markings, lobular atelectasis, emphysema, and bronchiectasis. Meconium ileus may be difficult to differentiate clinically from other forms of intestinal obstruction, but observations in these patients indicate that the diagnosis of meconium ileus may be established with certainty before surgical intervention by a simple test for the presence of protein. A protein material is readily precipitated from an aqueous extract of meconium on the addition of 10% trichloroacetic acid from the patients with meconium ileus, whereas little or no precipitate is formed from the extract of normal meconium. The clinical course of the patients after relief of their intestinal obstruction is similar to the course of patients with cystic fibrosis in whom the disease is detected months or even years after birth. The common belief that meconium ileus always means a poor prog-

nosis and represents the severest form of cystic fibrosis is not upheld. The degree of intestinal obstruction bears no direct relation to the ultimate outcome. After relief of the obstruction, the prognosis depends on the severity and rate of progression of the pulmonary lesion rather than on the intestinal and pancreatic dysfunction.

Laboratory investigations in these patients included the duodenal intubation usually performed during the first month and the thermal sweat test whenever practicable. The level of sweat sodium and chloride concentration noted did not correlate with the age of the patient or with the severity of the intestinal, pancreatic, or pulmonary process and had no prognostic significance. Results of the study of the duodenal fluid were characteristic of complete pancreatic insufficiency in all but one patient. The present condition of the 20 patients is summarized by stating that 5 are on or above the 50th percentile in weight, 7 patients are between the 20th and 50th percentiles, 4 are between the 3rd and 20th percentiles, and 4 are below the 3rd percentile. Inasmuch as the prognosis depends on the severity of the pulmonary lesion, an attempt is made to appraise this by clinical and roentgenologic study. Three patients appear to be free of pulmonary involvement, while six patients show mild, seven moderate, and two severe pulmonary involvement. There are two patients who fall between the moderate and severe groups. Patients may shift from one category to the next, and fortunately not always in the direction of increasing severity.

Treatment of Children with Acute Streptococcal Pharyngitis with a Single Penicillin Dose. H. Hartenstein and H. A. Feldman. J. Pediat. **48**:318-322 (March) 1956 [St. Louis].

This report is concerned with the use of a repository penicillin product, known as Panbiotic, that contains 600,000 units of benzathine penicillin G, 300,000 units of procaine penicillin G, and 300,000 units of buffered potassium penicillin G. The 1,200,000 units of penicillin in this mixture is in an aqueous suspension of 2 ml. volume which is administered by intramuscular injection. Early and adequate treatment of group A streptococcic infections is important with regard to the prevention of both acute rheumatic fever and glomerulonephritis, and penicillin is believed to be the drug of choice. Twelve children with acute upper respiratory tract disease, in 10 of whom it was proved to be due to group A streptococci, were treated with one intramuscular injection of Panbiotic. Clinical and bacteriological remissions were prompt, and there were no relapses. None of the patients developed subsequent acute rheumatic fever or acute glomerulonephritis. There were no untoward effects due to the drug except for mild tenderness and induration at the site of injection.

Chronic Ulcerative Colitis in Childhood. J. Holowach and D. L. Thurston. J. Pediat. **48**:279-291 (March) 1956 [St. Louis].

Chronic ulcerative colitis is comparatively rare in childhood. The 18 children whose cases are reviewed were observed at the St. Louis Children's Hospital between 1934 and 1953, when a total of 68,832 children were admitted. The case incidence of chronic ulcerative colitis in this institution was 0.026%, or 1 in 3,823 admissions. The age range of the 18 children was from 18 months to 14½ years, 13 being less than 7½ years old. The duration of symptoms before their first admission to the hospital ranged from five weeks to 10 years.

The symptoms and signs of chronic ulcerative colitis in childhood do not differ from those in adults except that the course in children is peculiarly stormy and malignant. Chronic ulcerative colitis may retard growth and development; this was evident in 9 of 16 patients, in whom retardation of physical development ranged from minus 1 to minus 4½ years. Seven of these nine patients showed more than two and one-half years' retardation of physical growth. In some of the patients sexual maturation was likewise retarded. Almost every known complication of chronic ulcerative colitis was observed in the 18 children. Some of these, such as arthritis, can be permanently disabling, as demonstrated in two of the patients. Surgery is mandatory in certain children, particularly in those with acute toxic ulcerative colitis and in those with threatening sequelae such as arthritis, severe growth failure, and malignant degeneration. Such surgery should entail colectomy and not ileostomy alone, and the colectomy should probably be complete. Such therapy is drastic, but even considering all the drawbacks it is the lesser of the two evils. Medical therapy should be reserved for mild to moderate cases, provided there are no serious complications and the course is not too prolonged.

The authors were able to follow 13 of the 18 patients, 11 of them for 8 to 21 years after the onset of the disease. The disease is now inactive clinically in four and chronically active in two. It was modified by surgical procedures in four and was fatal to three. Of the three deaths, one followed perforation of the colon and one attended an intestinal obstruction two years after the performance of an ileorectosigmoidostomy and colectomy; carcinoma of the colon was the cause of death in the other.

Bilateral Wilms' Nephroblastoma. G. B. Doyle. Arch. Dis. Childhood **31**:51-52 (Feb.) 1956 [London, England].

Doyle reviews the literature on bilateral Wilms' nephroblastoma and reports a case of a three-year-old girl who took a fall while playing in the road. Radiographs at the time of this mishap showed no abnormalities. In the next two months she had occasional bouts of vomiting, and her mother noticed a gradual enlargement of the abdomen. Urinary examination showed a few red blood cells in the uncentrifuged specimen. A roentgenogram of the abdomen showed a large opacity due to a mass of soft tissue. Shortly afterwards the child went into extreme shock and collapsed. An abdominal paracentesis was performed, and about half a pint of straw-colored fluid was aspirated. The patient's condition slowly deteriorated and she died. The abdomen contained a large tumor mass in the region of each kidney. Sections of both tumors showed the typical pattern of Wilms' nephroblastoma. Sheets of undifferentiated tissue of embryonic type surrounded clumps of epithelial cells in which there were tubules of varying development. The rarity of bilateral Wilms' tumor suggests that such cases as do occur are usually multifocal in origin and that direct extension from one kidney to another is unusual.

Thrombocytopenic Purpura and Chickenpox. R. G. Welch. Arch. Dis. Childhood **31**:38-41 (Feb.) 1956 [London, England].

Welch presents the histories of three patients (two children and one adult) in whom thrombocytopenic purpura developed from 10 days to five weeks after an attack of chickenpox. Thrombocytopenic purpura has been observed after many different types of infection on rare occasions, and it is thought that the most likely cause is an allergic response to the infecting organism. The condition is self-limiting, and the prognosis is usually favorable. One of the patients reported on also had a large hemangioma, and the combination of this growth with thrombocytopenic purpura has been reported previously.

Myasthenia Gravis: Four Cases. M. Latorre and R. Reynoso. Rev. chilèna pediat. **26**:471-476 (Nov.-Dec.) 1955 (In Spanish) [Santiago, Chile].

Myasthenia gravis is very rare in children. Four cases were observed during the last six years in the Luis Calvo Mackenna Hospital of Santiago, Chile. The patients were three boys between the ages of 7 and 14 years and a 10-year-old girl. The symptoms in all patients were similar, consisting of extreme fatigability, especially in the morning, palpebral ptosis, lowering of the angles of the lips, difficulty in deglutition and in speech, strabismus, and facial paralysis. The symptoms were more severe in the course of infections. The prostigmine test was positive in all. Mental and sensory reactions were normal. A roentgen examination of the thorax for shadows of persistent thymus was made in two cases, with a positive result in one case and a negative result in the other. The treatment consisted of prostigmine by mouth in doses of 15 mg. every six hours up to a total daily dose of 60 mg. This dose was maintained for a certain time and then it was progressively diminished until its discontinuation in, as a rule, about a year. The symptoms were controlled in all patients but one. They reappeared in this patient two years after the cure. They were due to strenuous physical effort during sport and were permanently controlled by administration of prostigmine on the above schedule for a short time. One of the patients, after

having experienced great improvement, developed acute respiratory disorders that did not respond to treatment. He died. Autopsy showed bronchopneumonia of the lower lobe of the left lung and diffuse hyperemia and hyperplasia of the thymus (thymus weighed 60 gm.). The other three patients were normal at the time of writing, from four to six years after the cure of the disease.

OTOLARYNGOLOGY

Coccidioidomycosis with Endolaryngeal Involvement. H. Singh, C. J. Yast and J. H. Gladney. A. M. A. Arch. Otolaryng. **63:** 244-247 (March) 1956 [Chicago].

The case presented concerned a 34-year-old Negro man who was admitted to the Hines Veterans Administration Hospital on Jan. 29, 1954. His presenting complaints were a productive cough of three months' duration and a hoarseness and dysphagia of one month's duration. A chest x-ray taken by his physician demonstrated multiple small pulmonary opacities of calcific density in the right hilar region. He was referred to the hospital for laryngoscopy because of a suspicion of laryngeal tuberculosis. The patient had served in the Army from 1942 to 1945 and was encamped in the California desert approximately 12 months of that time.

On examination, respirations were somewhat labored and were accompanied by laryngeal stridor. A bronzed circumscribed proliferative lesion was seen on the dorsum of the nose. A punched-out, dirty grayish, ulcerative lesion was seen on the distal phalanx of the left index finger. Indirect laryngoscopy revealed an extensive fungating granuloma involving the vestibule and endolarynx; the epiglottis was thickened and contained an ulcerative lesion of the laryngeal surface. There was considerable edema of both arytenoids and aryepiglottic folds, with distortion of the normal outline. The rima glottidis was slit-like and was almost completely fixed by the tumor mass. On the ninth hospital day tracheostomy was necessary because of increasing laryngeal stridor, and a biopsy specimen of granulomatous tissue was taken from within the trachea at the level of the third tracheal cartilage. The histological sections of this tissue were reported as demonstrating Coccidioides immitis. Subsequent biopsies of the cutaneous lesions of the nose and left index finger showed C. immitis in the histological sections. A complement fixation test for C. immitis was positive 41 days after admission. Chest x-rays on admission revealed calcifications in the right hilar region. X-rays of the left index finger revealed bony erosion along the lateral border of the distal portion of the terminal phalanx. Laminograms of the larynx revealed subglottic extension of the disease.

The patient received intravenous injections of 150 mg. of dihydroxystilbamidine four times daily for a total of 20 doses. Three months after completion of therapy there was healing of the cutaneous lesions. The structures of the endolarynx remained involved to a considerable degree, with the epiglottis, both ventricles, and true cords exhibiting extensive involvement. Resolution of edema and slight healing by scar formation resulted in widening of the rima glottidis, making tracheotomy no longer necessary. This is believed to be the first published report of coccidioidomycosis involving the structures of the endolarynx.

Primary Grafting of Fenestration and Mastoidectomy Cavities: Additional Experience with Primary Grafting of Fenestration, Modified Radical and Radical Mastoidectomy Cavities. B. T. Withers. A. M. A. Arch. Otolaryng. **63:**248-251 (March) 1956 [Chicago].

In 1952, the author had reported on results of primary grafting in 46 patients with radical mastoidectomy cavities. He utilized immediate split-thickness grafting in 33 additional cases. This group included 10 radical mastoidectomies, 8 modified radical mastoidectomies, and 15 fenestrations. Histological studies by Harbert and by Harris and Meadows indicated that a thin graft is more suitable than a thick graft approaching full thickness of the skin. The author's experience confirmed this concept. A cavity mold made from paraffin-petrolatum (Vaseline) gauze is advocated for "gloving" the skin graft for radical mastoidectomy cavities; for modified radical and fenestration cavities, strips of skin backed with rayon after Farrior's technique were used. No "sleeve" to protect the flap was required.

Results were as follows: 1. In radical mastoidectomy there was a dry ear in 8.6 weeks as opposed to 25.6 weeks in ungrafted cases. 2. In modified radical mastoidectomy and fenestration there was a dry ear in 6.5 and 4.2 weeks instead of the usual 12, 16, or 17.6 weeks in ungrafted cases.

A distinct improvement was made in the postoperative care of the donor site on the leg. Healing of the donor site is greatly facilitated by early "drying" treatment. At the end of 48 hours, the pressure dressing is removed from the leg and exposure to a standard heat cradle is started. The surgical rayon is left attached to the raw wound. Over a period of two to three days of dry heat, this strip becomes dried, disengages from the skin surface, and may be "teased" off painlessly by the patient. The patient then leaves the hospital on the fifth to the seventh day with the donor site covered with a dry scab. This gradually peels away and is replaced by new skin in approximately two weeks. The incidence of secondary infection in the donor site has been nil since the dry treatment was started. The healing time is almost cut in half.

THERAPEUTICS

Direct and Indirect Modes of Action of Salicylate Therapy. J. Roskam. Semaine hôp. Paris **32:**651-656 (Feb. 22) 1956 (In French) [Paris, France].

A review of the studies performed by a number of workers on the mechanism of action of the salicylates shows that certain facts have been established: Intensive salicylate therapy, provided it affords sufficiently elevated levels of salicylate in the blood and is prolonged over a sufficient period of time, produces a significant increase in the serum level of the 17-hydroxycorticosteroids. A daily dose of 8 gm. of a salicylate may produce this increase to the same degree as an injection of 20 mg. of delayed-action corticotropin. The hypercorticoidemia of salicylate therapy determines an increase in renal excretion of the 17-hydroxycorticosteroids and of the reducing corticoids; this manifestation is usually concomitant with the increase occurring in the blood level, but may be deferred. Hypercorticoidemia and hypercorticoiduria may persist after a reduction in dosage or even after discontinuation of the salicylate medication. It seems likely, because the intensity of the reaction is strong, that the increase in steroid metabolism is connected with the therapeutic effects of salicylate therapy in the collagen diseases and similar conditions. Animal experiments have shown that the salicylates have direct anti-inflammatory properties that are independent of stimulation of the adrenal cortex. Whether and to what extent such effects are operative in human beings remains to be established.

Evaluation of a New Anticoagulant, Acenocoumarin (Sintrom). M. Weiner, M. Jiminez and I. Katzka. Circulation **13:**400-403 (March) 1956 [New York].

Comparative pharmacological studies of hypoprothrombinemic agents made in the same group of individuals constitute a rational method of evaluating the properties of such agents and therefore also their probable advantages and disadvantages. This method was used in investigating a new coumarin compound, acenocoumarin (3-nitrophenyl-acetylethyl-4-oxycoumarin) (Sintrom). All known coumarin and indanedione anticoagulants apparently have the same fundamental mechanism of action, i. e., an inhibition of or alteration in the synthesis of a portion of the prothrombin complex. The differences in activity of these compounds are related primarily to (1) rate and completeness of absorption, (2) rate of metabolism and/or excretion, and (3) potency, or the amount of the drug needed to produce a given response. These factors can best be studied by determining the fate of each compound by chemical methods and correlating the result with the prothrombin response. Studies of this kind previously carried out in man with four compounds, bishydroxycoumarin (Dicumarol), ethyl biscoumacetate (Tromexan), phenindione (Danilone, Hedulin), and 3-α-phenyl-β-acetylethyl-4-hy-

droxycoumarin (Warfarin), have shown that (1) so-called therapeutic levels of prothrombin are rarely obtained in less than from 18 to 24 hours; (2) the duration of prothrombin response is directly related to the persistence of the drug in plasma, i. e., after a single intravenous dose, the more rapidly the drug disappears from the plasma, the shorter the duration of the response; (3) there are wide individual variations in the sensitivity of prothrombin response to a given drug plasma level, i. e., the same drug level in different subjects may result in quite different prothrombin time peaks; and (4) hypoprothrombinemic agents with relatively short duration of action tend to produce a more rapid initial prothrombin response, while those with prolonged duration of action produce hypoprothrombinemia more slowly. The speed with which a given prothrombin response is obtained also varies greatly with the dose given. Slow, long-acting hypoprothrombinemic agents can be given in doses large enough to induce a relatively rapid onset of response, but the use of such large doses may subsequently cause excessive prothrombin deficiency.

Sintrom is so potent that prothrombin response is the only basis on which it can safely be compared with other hypoprothrombinemic agents in man. The prothrombin response to various single doses of eight different hypoprothrombinemic agents was studied in five subjects. One week at least was allowed to elapse between recovery from the previous dose and administration of the next dose. The dose needed to obtain a peak prothrombin response of 23 seconds (control, 13.5 seconds) was thus determined for each drug in each subject. Sintrom was found to act at a rate very similar to that of phenindione, that is, it is distinctly more rapid than Dicumarol but somewhat slower than Tromexan. Its potency is considerably greater than that of Tromexan, phenindione, or Dicumarol.

Clinical experience with 444 patient-days of treatment in 15 subjects indicates that a desired degree of hypoprothrombinemia can be rapidly obtained and effectively maintained with Sintrom. Rapid fluctuations in prothrombin response making control difficult were noted in one patient only. All others were readily maintained in the desired range of prothrombin activity by daily doses of from 2 to 10 mg. No toxic manifestations were noted except for one case of hematuria, which was controlled by discontinuing therapy. The discontinuance of therapy results in a prompt return of prothrombin time to near normal in from one to two days.

Intra-Arterial Vasodilator Agents in the Treatment of Advanced Occlusive Arterial Disease of the Extremities: A Preliminary Report of a New Vasodilator Drug, 27 MI. O. A. Rose and A. Ebel. J. Am. Geriatrics Soc. **4**:142-150 (Feb.) 1956 [Baltimore].

Sixty-three patients with advanced occlusive arterial disease of the lower extremities were treated intra-arterially with the neutral thiophosphoric ester of 3-hydroxyphenyltrimethylammonium iodide trihydrate (27 MI) in doses of 5 to 20 mg. (10 mg. per cubic centimeter of isotonic sodium chloride solution). The drug was injected directly into the femoral artery below the inguinal ligament at a rate of about 10 mg. per minute. Peripheral arterial insufficiency had been caused by arteriosclerosis obliterans in 60 of these patients and by thromboangiitis obliterans in 2; and one patient had embolic occlusion of a femoral artery secondary to a myocardial infarct. The drug was well tolerated and there were no serious side-effects. Ischemic rest-pain, either in the presence or absence of concomitant necrosis or ulceration, was relieved in 58 patients (92%). The relief of pain was the most striking and consistent therapeutic effect of the drug. Healing of ulcers and necrosis appeared to be expedited by this method of treatment. In 10 normal men who served as controls, the administration of 27 MI resulted in maximum vasodilation, which occurred predominantly in the skin, but without apparent reduction in muscle blood flow. Intra-arterial administration of 27 MI, which proved to be a safe and effective vasodilator agent, appears to be of particular value in the treatment of patients with advanced arterial disease involving the lower extremities, particularly when there is concomitant vascular disease in other areas and when the patient's general condition is considered to be too precarious for the administration of generalized vasodilators.

RADIOLOGY

Paraplegia, Rare Complication of Translumbar Aortography. B. S. Abeshouse and A. T. Tiongson. J. Urol. **75**:348-355 (Feb.) 1956 [Baltimore].

A rare complication of translumbar aortography characterized by sudden onset of paraplegia with areflexia, thermanesthesia, and loss of bladder and rectal control is described. The complication occurred six hours after the injection of a 70% solution of Urokon sodium into the abdominal aorta. The procedure was performed in the usual manner, and all the customary precautions were taken. The patient died 16 months later of generalized carcinomatosis after having shown gradual and progressive improvement in his neurological condition. Although this is only the fourth authentic case reported in the literature, the authors are inclined to believe that the true incidence of this complication is greater than the reports indicate. They think that the cause of the paraplegia was spinal cord changes produced by direct toxic action of the highly concentrated contrast medium, which reached the spinal cord through the anterior spinal arteries and their collateral branches. The principal alteration seen in the spinal cord at autopsy was demyelination. The possible causal role of transient or permanent vasospasm or thrombosis of the spinal artery cannot be excluded; however, no evidence of these was found on pathological examination of the affected tissue. Translumbar aortography is a relatively safe and simple procedure, but its possible complications must always be weighed against its value as an aid to diagnosis in each particular instance.

The Use of Dionosil in Bronchography: A Preliminary Report. C. M. Nice Jr. and M. Azad. Radiology **66**:1-8 (Jan.) 1956 [Syracuse, N. Y.].

The authors list the requirements of agents to be used in contrast roentgenography and say that in their opinion these criteria have been fulfilled best by *n*-propyl 3:5-di-iodo-4 pyridone-N-acetate (propyliodone), which is manufactured under the trade name of Dionosil. They report the results obtained with this contrast medium in 74 bronchographic examinations in 68 patients. They found no unusual irritability with either aqueous or oily suspensions of this substance. The medium permits unhurried examination, and bronchograms of good diagnostic quality are easily obtained. There is little tendency for propyliodone to produce extensive alveolar filling. In most patients, only a trace of the propyliodone remains in the pulmonary field three days following bronchography. Many advantages, and no disadvantages, are noted when this substance is compared with the iodized oils and Xumbradil Viscous B for bronchography.

Body-Section Cholangiography with a New Intravenous Medium (Cholografin). A. L. L. Bell, L. L. Immerman and J. Arcomano. Radiology **66**:84-87 (Jan.) 1956 [Syracuse, N. Y.].

In the course of investigations with a new cholecystographic agent, Cholografin, it became apparent that the presence of confusing shadows in the right upper abdominal quadrant, produced by overlying feces and gas, could be eliminated by the use of body-section techniques. The examination is performed on the planigraphic table so that, as the concentration within the duct system approaches maximum, usually after about 40 minutes, planigraphy of the right upper quadrant can be begun. Since the common bile duct lies approximately in the midcoronal plane, a starting point corresponding to this is chosen. Films are then made at 1-cm. intervals from this point until maximum definition of the duct system is obtained. Regardless of the projection used, anteroposterior or right posterior oblique, 3 to 4 sections will usually suffice to delineate the duct system. Using these methods, the authors were able to standardize a technique comprising an average of eight or nine exposures, including a preliminary film and body-section films. This combination of body-section radiography with intravenous cholangiography has been used in over 50 patients after cholecystectomy. The method has the advantages that it (1) eliminates overlying densities that may be confused

with an intraluminal filling defect; (2) demonstrates the intrahepatic and extrahepatic bile ducts even with poor concentration of contrast medium; (3) reveals the presence of stones within the duct system; and (4) clarifies anatomic conditions that have been altered by operations on the biliary tract. The authors believe that radiologists should use such techniques routinely whenever intravenous cholangiography is performed.

Radiological Treatment of Primary Bronchial Carcinoma. E. Poppe. Tidskr. norske laegefor. **76**:1-5 (Jan. 1) 1956 (In Norwegian) [Oslo, Norway].

Radiological treatment is not indicated for radioresistant forms of bronchial carcinoma either for palliative purposes or postoperatively. In the radiosensitive forms, combined surgical-radiological treatment of the operable cases may give better results than surgery alone, and in the inoperable cases radiology may have good palliative effect. The slightly differentiated forms of bronchial carcinoma may be highly radiosensitive and are extremely malignant. Preoperative or postoperative radiotherapy will probably improve the results of treatment in these forms of cancer; the inoperable cases should be given palliative radiotherapy. It is difficult to determine whether radiotherapy improves the results of radical surgical treatment in flat epithelial carcinomas, which are somewhat radiosensitive; on the basis of his experience, the author advocates postoperative radiotherapy.

The patients referred for radiotherapy of bronchial carcinoma most often have an advanced inoperable tumor and they may be febrile, with affected general condition. There is usually infection in the lung peripheral to the tumor, and antibiotics must be given at the outset. Repeated blood transfusions are important. Treatment of bronchial carcinoma with Betatron offers important advantages over treatment with conventional radiation. Betatron operates with 31 million volts, the roentgen rays produced have a considerable penetrative quality, and as the spread is far less than with conventional roentgen irradiation the treatment is less injurious to the surrounding tissue. For operable cases it is possible that Betatron given preoperatively or postoperatively can better the results; in the inoperable cases where the tumor belongs to the radiosensitive group, a palliative effect is hoped for.

Orientation in the Surgical Treatment of Chronic Constrictive Pericarditis in the Light of Angiocardiographic Findings. A. Actis-Dato and F. Morino. Minerva med. **47**:6-18 (Jan. 6) 1956 (In Italian) [Turin, Italy].

The angiocardiograms of 12 patients with constrictive pericarditis were studied preoperatively in an attempt to evaluate the anatomic and morphological changes induced by the constrictive process on the heart chambers and the great vessels, to discover eventual vascular alterations of the pulmonary circulation, to demonstrate the type and extent of the hemodynamic alterations present, and to localize, if possible, the heart sector or sectors in which the constrictive process was most marked and the need for pericardiectomy greatest. The results of the angiocardiograms were compared with the clinical, roentgenographic, surgical, and, in two instances, autopsy findings. They were also compared, in six patients, with the pressure values within the heart chambers as recorded by cardiac catheterization. In general, the angiocardiograms revealed hemodynamic atrioventricular impediment and indicated that constriction of the heart by a fibrosclerotic pericardium has main functional repercussions on the ventricles. These repercussions manifest themselves with adiastole and hyposystole. The ventricular adiastole is confirmed on the angiocardiograms by a normal, or smaller than normal, volume of the ventricle, in contrast with ectasia, often pronounced, of the atrium. Hyposystole of the right ventricle is confirmed by the few slight signs of arterial stasis of the pulmonary circulation, and that of the left ventricle by the more or less marked reduction of the systolic output, observed in all of the patients. The angiocardiograms indicated that in patients with constrictive pericarditis the function of the left ventricle is impaired oftener or at least to a greater extent than the function of the right ventricle. This study was of great value in that it indicated that the cause of the cardiovascular insufficiency present in these patients lies in the ventricles, and especially in the left ventricle. In none of these patients was a hemodynamic obstacle found at the mouth of the venae cavae. This study seems to support the theory of Prof. A. M. Dogliotti, who at his Turin clinic treats patients with constrictive pericarditis by sectioning and removing the pericardium over the left ventricle and extends the operation to the left atrium and the anterior aspect of the right ventricle only when necessary. The results of this angiocardiographic study seem to indicate that Dogliotti's partial pericardiectomy is the treatment of choice for patients with constrictive pericarditis.

PHYSIOLOGY

Experiments on the Comparative Nutritive Value of Butter and Vegetable Fats. L. P. Dryden, J. B. Foley, P. F. Gleis and A. M. Hartman. J. Nutrition **58**:189-201 (Feb.) 1956 [Philadelphia].

Apart from known differences in fat-soluble vitamin content, the nutritive value of butterfat as compared to vegetable fats has been a subject of dispute for a number of years. The authors made experiments on female albino rats. Comparisons at 4 different fat levels were made between butterfat and corn oil incorporated into lactose-containing diets fed to weanling rats. Growth on the butter rations increased with increasing fat level. Growth on the corn oil rations showed the same tendency but not to a significant degree. Only at the higher fat levels was there evidence to indicate that butter promoted weight gains superior to those obtained with corn oil. Supplementation of the butter diet with linoleate had no effect. A comparison between the growths of rats fed summer or winter butter at three different fat levels showed no differences at any level over an 18-week period.

Comparisons were made between butterfat, margarine fat, and corn oil incorporated into sucrose rations containing 28% fat. Butterfat and margarine fat were found to promote significantly better growth of weanling rats than corn oil but only during the first three weeks of the experiment and when Sulfathalidine was included in the ration. The suggestion has been made that in experiments of this sort butterfat may supply an unidentified nutrient that is not present in corn oil but that may be supplied by intestinal synthesis in the absence of Sulfathalidine. It is also possible that the effect of the fat is more indirect. Thus butterfat may counteract to some extent the effect of Sulfathalidine in preventing the synthesis of such a nutrient.

Ascorbic Acid Utilization by Women: Response of Blood Serum and White Blood Cells to Increasing Levels of Intake. E. H. Morse, M. Potgieter and G. R. Walker. J. Nutrition **58**:291-298 (Feb.) 1956 [Philadelphia].

This study concerns the relationship between the ascorbic acid level in the blood serum and that in the white blood cells of a group of women on graded levels of ascorbic acid supplementation. The average blood serum ascorbic acid level in 19 women subjects fell from 0.97 mg. to 0.47 mg. per 100 ml. of serum during a period of six weeks on a diet containing an average of 33 mg. of ascorbic acid per day. The average serum level increased to 0.74 mg. after five weeks on an intake of 58 mg., to 1.47 mg. after five weeks on an intake of 83 mg., and to 1.69 mg. after an equal period on 133 mg.

Fluctuations in white blood cell levels were consistent with those in the serum though somewhat less marked. During the period of restricted intake, the average white blood cell level for the subjects fell from 29.94 mg. to 19.55 mg. of ascorbic acid per 100 gm. of white blood cells. After the first two periods of supplementation, the white blood cell level rose to 26.67 mg. and 34.55 mg. respectively. There was no further increase in white blood cell ascorbic acid level as a result of increasing the intake to 133 mg. per day. Statistical analysis of the data indicates that, with intakes between 33 and 83 mg. per day, under the conditions of the present study, the average serum level was a reasonably good indicator of the average ascorbic acid content of the white blood cells.

BOOK REVIEWS

The Nonvenereal Diseases of the Genitals: Etiology, Differential Diagnosis and Therapy. By Fritz T. Callomon, M.D., and John F. Wilson, B.S., M.D., M.S., Assistant Professor, Dermatology and Syphilology, Jefferson Medical College, Philadelphia. Cloth. $12.50. Pp. 382, with 150 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

It may seem trite to state that this book fills a long-felt need, but it does that precisely, and in commendable fashion. It is the first book in English on the subject. There were German editions by the senior author in 1924 and 1928. There are three parts to the book, two dealing with cutaneous and subcutaneous diseases affecting the genitalia and the third covering diseases of the lower urogenital tract. The scope is comprehensive, covering all phases but especially the cause, differential diagnosis, and treatment of all types of infections, affections, atrophies, ulcerations, neoplasms, etc. The genital manifestations of diseases such as Behcet's and Stevens-Johnson syndromes and of other systemic diseases and of rare conditions are considered fully. Thirty-eight pages are devoted to nongonococcic urethritis. There is a chapter devoted to general therapy that is up-to-date. The illustrations are in black and white. Nonvenereal diseases affecting the genitals are more often than not neglected in medical teaching. This book, covering the subject as it does, comprehensively and with authority, should be well received by practically all practitioners.

Atlas und Praktikum der Dermatologie und Venerologie. Von Professor Dr. med. W. Burckhardt, Leiter der städt. Poliklinik für Haut- und Geschlechtskrankheiten, Zürich. Cloth. 48 marks; $11.50. Pp. 279, with 164 illustrations. Urban & Schwarzenberg, Thierschstrasse 11, Munich 26; Meinekestr. 13, Berlin W. 15, Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1955.

American dermatologists may well be envious of European colleagues who are able to publish an atlas with 100 good color plates and still keep the price within reasonable limits. The author is internationally known for his work on the buffering capacity of the skin and its relation to alkali sensitivity. His present work is directed to the general practitioner, and from this point of view the illustrations of common dermatoses are well selected. With a few exceptions (plate 65 on lichen planus and plate 75 on pityriasis rosea are not very characteristic), the pictures are excellent and should be helpful in general practice. The text is short, but the material is well selected, and many important diagnostic points are well taken. The chapter on allergic dermatoses is excellent. With some points most American dermatologists will disagree. Butcher's pemphigus is listed with other varieties of pemphigus, although it is known to be a micrococcic (staphylococcic) septicemia. Seborrheic warts (the author's "verruca senilis") are listed among infectious acanthopapillomas although they never have been proved to be infectious. For temporary epilation of the scalp, thallium acetate is said to be acceptable if x-ray epilation is not feasible. For the treatment of psoriasis and lichen planus, arsenic is still listed among the recommended therapeutic procedures. In systemic moniliasis the recommended high doses of potassium iodide are ineffective in the experience of American authors. Penicillin and sulfonamide ointments are still used in Europe in treatment of pyodermas, but American dermatologists discarded them long ago because of their high sensitizing potentialities. It seems that antibiotics that apparently do not sensitize in local application, such as bacitracin, neomycin, and polymyxin, had not yet reached the practitioners in Europe when this book went to press. These, however, are minor points.

The only serious criticism concerns the multitude of therapeutic recommendations. Not only does the book not contain any warning against "overtreatment" of acute and subacute inflammatory processes but it almost encourages such a tendency. For instance, for prevention of superinfection in herpes simplex the book recommends ammoniated mercury, chlortetracycline, and oxytetracycline ointments or cinnabar powder. Herpes simplex notoriously does not tend to be secondarily infected and the best treatment is to leave it alone or, if anything is to be done about it, it is covered with zinc oxide ointment. For the American reader it is also somewhat disturbing that many remedies are mentioned only by their proprietary names without the statement of their chemical composition. On the whole, however, the book is a valuable contribution and recommended to all general practitioners who read German.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

Hypothalamic-Hypophysial Interrelationships: A Symposium, Third Annual Scientific Meeting of Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and edited by William S. Fields, Professor of Neurology, Roger Guillemin, Assistant Professor of Physiology, and Charles A. Carton, Assistant Professor of Neurological Surgery, Baylor University College of Medicine, Houston. Cloth. $4.75. Pp. 156, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1956.

Until relatively recently the hypothalamus received little or no attention in clinical and relatively little even in physiological literature, but recognition of its importance as a regulating organ in the animal economy has stimulated numerous physiological studies defining this relationship. The topics discussed include Neural Pathways to the Hypophysis (J. D. Green); Neurosecretion in the Central Nervous System (W. Hild); Hypothalamic Control of the Anterior Lobe of the Hypophysis (G. W. Harris); Hypothalamic-Hypophysial Interrelationships in the Production of Pituitary Hormones in Vitro (R. Guillemin); The Relation Between Anterior and Posterior Hypophyses and the Hypothalamus in Response to Stress (M. Stein and I. A. Mirsky); Telencephalic Influences upon the Hypothalamus (P. Gloor); Steroid Hormonal Response to Stimulation of the Brain (J. L. Pool and others); and Hypothalamic-Hypophysial Dysfunction in Man (C. L. Spurr and S. H. Stribling). Each paper is followed by a discussion. The book has been carefully edited and printed in an excellent format. It will be of primary interest to those engaged in research in this field but is too technical to appeal to the general reader.

The Diagnosis and Management of Urological Cases: A Handbook for Students, Residents and General Practitioners. By Bruce W. T. Pender, M.B., B.S., F.R.C.S., Senior Surgical Registrar, St. George's Hospital, London, and James O. Robinson, M.A., M. Chir., F.R.C.S., Senior Surgical Registrar, St. Bartholomew's Hospital, London. Foreword by Sir W. Heneage Ogilvie, K.B.E., M.A., M.D., Consulting Surgeon, Guy's Hospital, London. Cloth. $5. Pp. 170, with 48 illustrations. Baillière, Tindall & Cox, 7-8 Henrietta St., Covent Garden, London, W.C.2, England; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

This book presents the more common urologic procedures to the student and general practitioner of medicine. Brevity takes precedence over completeness. The book is divided into seven short chapters in which the illustrations are schematic drawings. The first chapter deals with the history, examination, common laboratory procedures, instruments, and the various urinary antiseptics. It follows the usual pattern of such chapters. The prostate is discussed in chapter 2. Immediate emergency prostatectomy without preliminary cystoscopy is advocated for patients with uninfected acute urinary retention with normal renal function. The retropubic route is favored. Preliminary indwelling or intermittent catheterization plus chemotherapy is suggested in the treatment of patients unfit for immediate prostatic surgery. Carcinoma of the prostate with obstruction can be treated satisfactorily in most cases by large doses of estrogens and temporary catheter drainage rather than operation. Many urologists would not concur with the authors in their management of bladder neck obstructions.

Most of the third chapter is a discussion of urethral strictures with nothing unusual presented. The fourth chapter deals with the common diseases of the bladder such as tumors, infections, stones, injuries, and diverticula. There are also a few paragraphs on the neurological bladder. The suggested regimen of intermittent catheterization for the paraplegic patient has long been condemned by authorities in this country. Certainly intermittent catheterization is not necessary once an automatic bladder has developed. Large bladder stones are removed suprapubically. An interesting point on litholapaxy is that the authors perform it with the bladder empty. In chapter 5 the common diseases, including congenital anomalies of the kidney and ureter, are discussed. The authors believe lumbar and renal sympathectomy to be of value in treatment of moderate idiopathic hydronephrosis; this statement would be questioned by many urologists. The discussion on kidney and ureteral calculi is sketchy and in some instances departs from the usual accepted ideas on this subject.

Chapter 6 contains short and concise statements on various diseases of the penis and scrotum such as balanitis, phimosis, carcinoma, hydrocele, epididymitis, testicular tumors, and undescended testes. The authors suggest repeated aspirations of a hydrocele instead of operation in older men. In the management of undescended testes, orchiopexy is suggested at an older age than most authorities advocate. Chapter 7 concerns genitourinary tuberculosis. The discussion of treatment follows the same line of thought as in this country. There is a short appendix in which are listed normal values for various laboratory tests, doses of common drugs, and a description of the different types of drainage systems used in urology. There is no bibliography. Although this publication falls far short of presenting all the factors involved in disease of the genitourinary system, it might be of value to the busy practitioner who is looking for guidance in some of his urologic problems.

The Diabetic Life: Its Control by Diet and Insulin. A Concise Practical Manual for Practitioners and Patients. By R. D. Lawrence, M.A., M.D., F.R.C.P., Physician in charge, Diabetic Department, King's College Hospital, London. Fifteenth edition. Cloth. $3.50. Pp. 228, with 19 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W.1, England, 1955.

Although this manual, written by England's foremost and most experienced specialist in the field, contains the information required by all diabetics set forth in a conscientious and thorough fashion for laymen, most physicians could read it with profit. Its educational level is moderately advanced scientifically. The book is beautifully printed and bound, but sparsely illustrated. Its appendix is devoted largely to testing methods and its last few chapters, as usual, to dietary detail.

Mental Disorders in Later Life. Edited by Oscar J. Kaplan. Second edition. Cloth. $7.50. Pp. 508, with 23 illustrations. Stanford University Press, Stanford, Calif.: Oxford University Press, Amen House, Warwick Sq., London, E.C. 4, England, 1956.

An expanded and revised edition of a good book is always welcome. This is especially true when, like this one, it is the only one of its kind, is timely, and has as authors for its 18 chapters men who have been chosen for their original or pioneer work in the general field with which this volume deals. The mental diseases of later life have increased in relative and absolute numbers. Present trends indicate that all physicians and most specialists will find an increasing proportion of such patients in their practices. This book is intended to decrease the air of hopelessness with which the mental disorders of older persons are regarded, encourage more energetic and scientifically oriented treatment of them, and promote interest in their further study. The book succeeds in doing so by the interest it awakens and the documented reasons for optimism it presents.

The first edition of this book appeared in 1945. To the basic chapters on the physiological, sociological, and psychological aspects of the mental disorders of later life by Shock, Dunham, Jones, and Kaplan has been added a new chapter on the genetic aspects by Kallman that, together with the excellent statistical review by Malzberg, comprise a fine introduction to the subject. Senile psychoses and psychoses with cerebral arteriosclerosis are dealt with in a clear, comprehensive, and judicious manner by Rothschild, who has shown that there is no absolute correlation between clinical behavior and cerebral damage. The presenile dementias are ably discussed by Jervis. That the toxic deliriums of old age are reversible is well documented by Robinson. This author appears to be unduly impressed by the relationship between these disorders and liver damage, but this contentious thesis makes the chapter all the more stimulating. The chapter by Cameron on the neuroses of later maturity is an exceptionally clear review of the basic theory, genesis, and treatment of maladjustment in older persons. In his discussion of the so-called involutional psychoses Davidoff places greater faith in hormonal therapy than do many others but in all presents a well-balanced view in which the efficacy of electric shock in properly selected patients is stressed and the diagnostic value of this procedure is properly stated. That electric shock treatment can be used safely in aged patients even though there may be severe cardiovascular or skeletal disease is amply documented by Prout and his associates. This is the second new chapter in the book. The authors recommend premedication with curare and sedatives in selected patients. An interesting report on older mental patients after long hospitalization is made by Hanfman, who stresses that mental hospitals are active treatment centers but also can be adequate domiciles for patients who must remain for many years or a lifetime. She emphasizes the provision of opportunities for healthy socialization and productivity as well as the provision of incentive to work by payment even though it be nominal in amount. There are further chapters on nutrition, the aged abnormal, psychosomatic medicine, psychotherapy, mental hygiene, and a brief introduction as well as a summarizing chapter on orientation of the problems.

This collection of essays does not pretend to be a textbook nor an exhaustive treatise. It cannot be considered as representative of the latest advances or as describing psychiatric technique for the specialist. The book is an excellent introduction to the subject. Those well acquainted with the field should find it a good review. Each chapter shows evidence of scholarship and judgment and has a good list of references. Good editing has kept the chapters independently complete with a minimum of boring and time-consuming overlap. The book is recommended to the reader in general medicine and to specialists in geriatrics and psychiatry. The print is clear, and the book is a handy size. The index is poor and consists for the most part of names. It is regrettable that the editor did not insist on use of the newer psychiatric nomenclature throughout the book.

Nursing Care of the Newly Born Infant. By W. S. Craig, B.Sc., M.D., F.R.C.P., Professor of Pædiatrics and Child Health, University of Leeds, Leeds, England. In collaboration with M. F. G. Buchanan, M.B., Ch.B., M.R.C.P., R. J. Pugh, M.B., Ch. B., M.R.C.P., and Miss M. Pattullo, R.G.N., S.C.M., Departmental Sister, Maternity Hospital, Leeds. With chapter on Mothercraft, contributed by Miss M. J. W. Taylor, R.G.N., S.C.M., M.T.D., Matron, Jessop Hospital for Women, Sheffield. Cloth. $7. Pp. 472, with 225 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

The central theme of this book is the importance of observations by professional personnel of the many signs and symptoms of the normal and the abnormal in the newborn infant. Written in Great Britain, this book is intended primarily for the midwife and family physician but is also directed toward all nursing and medical personnel faced with the care of the newborn child. Throughout, an effort has been made to allow for contrasting conditions of domiciliary and hospital practice and to encourage the study of illness and abnormal development against a background of health. The illustrations (many in color) effectively promote the ready recognition of the signs and symptoms of health and disease in the early days of life. Much attention is given to the feeding of the infant. Other subjects discussed include minor departures from normal in the newborn infant, trauma, infection, congenital anomalies, prematurity, emergencies and their immediate management, and special nursing procedures. This book is particularly notable for the wholesome and intelligent attitude it promotes toward the professional care of the newborn infant and for its excellent illustrations. It is recommended for reading and reference for those professional groups for whom it was written.

QUERIES AND MINOR NOTES

INFANT WITH PARALYTIC POLIOMYELITIS

To the Editor:—*A 7-month-old infant had onset of paralytic poliomyelitis two weeks ago. The condition involves both legs and the right leaf of the diaphragm, although there is slight paradoxical movement of the right leaf of the diaphragm. This patient's cry is weaker than usual; there is no tachycardia, no dyspnea, no flaring of ala nasi, no cyanosis in air, and the child is playful. There is no atelectasis of the right lung. Should I place this child in a respirator? Is it wrong not to place him in a tank-type respirator? Should he be kept in it intermittently or constantly?*

Charles L. Concklin, M.D., Corpus Christi, Texas.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—A respirator is probably not necessary routinely, considering the difficulty of such procedures in a small infant. However, the child should be watched closely, particularly during sleep, and if he becomes cyanotic he should be placed in a respirator for sleep. The tank respirator is unnecessary, unless for the above condition, when the small-size type will be more satisfactory. The child should have deep-breathing procedures three times a day by intermittent positive pressure at the upper airway. This is to prevent atelectasis.

Answer.—With an infant 7 months of age it is for all practical purposes impossible to get adequate readings of vital capacity, and clinical observation is the most valuable method of determining respiratory needs. If the child is playful and eating well, with no flaring of ala nasi, there would be no need for any respiratory assistance. It is believed that when respiratory assistance is needed in acute poliomyelitis it must be given in a tank respirator. The rocking bed and chest respirator should be used only as weaning devices. Should an upper respiratory or other illness develop, the child must be carefully watched for some respiratory insufficiency and placed in a tank respirator temporarily.

TONSILLAR HEMORRHAGE

To the Editor:—*I would like to know the cause, prevention, and treatment of bleeding tonsils.*

M. J. Schirber, M.D., Grand Rapids, Minn.

Answer.—Tonsillar hemorrhage may occur either at the time a tonsillectomy is performed or at some time after the operation. The tendency to bleed may be due to blood dyscrasias, prolonged bleeding time, prolonged coagulation time, diabetes, cardiac disorders, or syphilis. Patients who are about to undergo tonsillectomy should always have a complete physical examination before the operation, for it is unwise to assume that patients are in excellent physical condition and that no contraindications to surgery exist. The best way to prevent complications is to rule out factors that might produce difficulties at or after the operation. At the time an operation on tonsils is performed, hemorrhage can result from excessive trauma of the tonsillar bed, the presence of adhesions, an aberrant artery or branch of the external carotid artery that has been severed, or haphazard clamping of the blood vessels. Tonsillar hemorrhage that occurs postoperatively may be due to active bleeding from a blood vessel, incomplete removal of tonsillar tissue, the presence of a blood clot in the tonsillar fossa, or oozing from the tonsillar bed. In most instances postoperative hemorrhage can be effectively controlled by ligation of bleeding blood vessels, removal of clots from the affected tonsillar fossa, pressure exerted at the site of oozing, and the topical application of hemostatic agents. There are other procedures, but the ones mentioned are the most common. In general, tonsillar hemorrhage can be avoided or overcome by diligent adherence to well-established safeguards and procedures.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

TEST FOR SERUM BILIRUBIN

To the Editor:—*I would appreciate a report on the method of clinical evaluation for a one-minute test for total serum bilirubin.* *Arthur J. McSteen, M.D., Greensburg, Pa.*

Answer.—Bilirubin is formed by the destruction of hemoglobin from disintegrated erythrocytes in the reticuloendothelial system. It is formed in the endothelial cells in combination with protein or in a colloidal state and passes into the blood stream; it cannot be excreted by the kidneys in this form. It gives the characteristic bilirubin reaction of van den Bergh only after precipitation of the protein by alcohol. This is called the indirect reaction of van den Bergh. Blood serum, 0.25 ml., is added to each of three small test tubes. Then, 0.2 ml. of diluted hydrochloric acid is added to one tube, and 0.2 ml. of freshly prepared diazo reagent is added to another. These are mixed, and the time is noted for the development of any color. After five minutes, 0.2 ml. of diazo reagent is added to the third tube and compared with the two control tubes to determine the time of the development of the maximum color. An immediate reaction is shown by the development of color before 30 seconds has elapsed. A reaction is negative when no color develops in 30 seconds. A delayed or negative reaction may be obtained in both normal serums and serums from patients with nonobstructive or hemolytic jaundice. Normal blood contains from 0.1 to 0.5 mg. of bilirubin per 100 ml. The renal threshold for bilirubin is about 2 mg. per 100 ml. of blood. In hemolytic jaundice, the bile pigments cannot be separated from the plasma by the kidney so that none appear in the urine. In obstructive jaundice the bile pigments are separated from the plasma by the liver but cannot be excreted into the duodenum. They are reabsorbed into the blood stream and excreted into the urine. This point is used in differential diagnosis.

HYSTEROSALPINGOGRAPHY

To the Editor:—*I would like information regarding the use of hysterosalpingography using a contrast medium in a patient with the following conditions: suspected pregnancy, tubal or ectopic pregnancy, and adenocarcinoma of the fundus of the uterus.* *M.D., Minnesota.*

Answer.—Although hysterosalpingography has been carried out in the pregnant patient and in the patient suspected of ectopic pregnancy, it has not enjoyed universal approval. The majority expressing themselves feel that the danger of interfering with a normally implanted pregnancy or danger of rupturing an ectopic pregnancy makes the risk too great. The test for pregnancy should obviate the necessity for diagnosing a normally implanted fertilized egg. Colpotomy or colpocentesis, aided in some instances by culdoscopy, should obviate the necessity of its use in diagnosing ectopic pregnancy. As to the use of the procedure in the diagnosis of adenocarcinoma of the endometrium, it has been proved to be of diagnostic value in a high percentage of cases. There is, however, the danger of forcing desquamating tumor cells into the fallopian tubes or directly into the peritoneal cavity, thus causing extension of the disease. Aspiration curettage or diagnostic curettage is a more accurate procedure and less dangerous. Davids (*Am. J. Obst. & Gynec.* **65**:1167, 1953) discusses the appearance of the uterus with endometrial carcinoma. References discussing the use of the method in diagnosing ectopic pregnancy are not common. Lawrence

(*Brit. J. Radiol.* **25**:161, 1952) and Schneider and Eisler (*Zentralbl. Gynäk.* **51**:1360, 1927) have discussed the findings and techniques involved.

OVULATION

TO THE EDITOR:—*A woman menstruating regularly supposedly produces only one ovum per cycle. How is this regulated? Do the ovaries alternate in producing ova? When a woman has one ovary removed and menstruation and, presumably, ovulation continue regularly, does the remaining ovary produce one ovum each month? What is the consensus regarding the accuracy of basal temperatures in determining the time of ovulation? In one book on gynecology, it is stated that some women ovulate only during menstruation. How can this be explained?*

M.D., Kansas.

ANSWER.—A young woman who has a fairly regular menstrual pattern ovulates each month and usually releases one ovum per cycle. There are little accurate data on humans concerning the ovary in which ovulation occurs. In laboratory animals who have multiple ovulations, both ovaries participate at each ovulatory period. However, women who exhibit some discomfort at the time of ovulation (mittelschmerz) find that this discomfort alternates fairly regularly from one side to the other. This would indicate that ovulation occurs alternately in each ovary. If one ovary is removed, ovulations continue to occur monthly from the one ovary. In all likelihood, the gonadotropic hormones from the anterior lobe of the hypophysis provide a quantitative stimulus usually sufficient for one follicle to reach complete maturity and to ovulate. If one ovary is removed, the remaining gonad is subjected regularly to the same quantitative pituitary stimulus. The body basal temperature is an excellent clinical guide to ovarian activity. If a woman who leads a fairly regular life will take her temperature orally immediately on awakening each morning and record it promptly, the resultant graph will indicate whether she ovulates and the approximate time of ovulation. It is not often possible to pinpoint the exact day of ovulation, although it often occurs at the lowest level of temperature at the onset of the ovulatory rise. Most often it is well to regard the period of transition from the low preovulatory level to the elevated postovulatory level as the ovulatory phase. Thus, ovulation can be limited to a two or three-day period in the cycle. It is a gross inaccuracy to state that women ovulate only during menstruation. A menstrual period may or may not be ovulatory in character, but, in the human, ovulation rarely occurs during the menstrual phase.

EFFECT OF WETTING AGENTS ON METABOLISM

TO THE EDITOR:—*I am confused about the effect of wetting agents, e. g., polysorbate 80 and dioctyl sodium sulfosuccinate, given orally, on the assimilation and metabolism of fats and cholesterol. Please give a résumé of what is known about this subject, and also, if possible, what their effect is on atherosclerosis.*

Lyman C. Blair, M.D., Houston, Texas.

ANSWER.—During the normal absorption of lipids, some may pass through the intestinal mucosa in an unchanged form but the greater part is first hydrolyzed into its component fractions. For either process, a fine emulsion is necessary: fat droplets must be tiny either to pass the intestinal barrier or to offer an adequate surface to hydrolytic enzymes. Any wetting agents, consequently, might improve fat absorption by their property of enhancing and stabilizing emulsions. In practice, the theoretical usefulness of the wetting agent is not realized. Normal lipid absorption is already so efficient that it cannot be enhanced. In patients with impaired fat absorption (sprue, pancreatic insufficiency, biliary obstruction, or gastrectomy), wetting agents given by mouth have been found useful by some but the general experience has proved disappointing. Theoretically, these agents should prove most useful when bile salts, the natural "wetting agents," are absent. Yet, polysorbate 80 does not improve fat absorption in dogs with complete biliary obstruction. The effect of giving wetting agents to patients with atherosclerosis remains uncertain as long as the pathogenesis of this disorder is unclear. The theoretical action of wetting agents in enhancing fat absorption would not appear beneficfal for atherosclerosis. A small amount of orally administered polysorbate 80 is absorbed (less than 5%). No evidence is available that this amount stabilizes or changes human plasma lipids with the specific result of preventing atheromatous deposits. Even if the gross character of plasma lipids can be altered (such as decreasing alimentary lipemia), the benefit thereby achieved is questionable. Finally, the combination of wetting agents with lipotropic factors is difficult to support as sound therapeutic practice. By and large, lipotropic factors that mobilize fat from a "sick" liver have not been shown to mobilize lipids from a "sick" artery.

FIRST-AID CABINET FOR SMALL FACTORY

TO THE EDITOR:—*Please supply a list of the items needed to equip a first-aid cabinet for a small factory employing about 40 men, with no nurse or other trained person available. The factory owner has always been prompt to send injured employees to a physician's office or hospital for treatment and expects to continue to do so.*

M.D., Ohio.

ANSWER.—The supplies recommended by one of the large insurance companies for an industry with 25 to 50 employees are listed in the table.

Supplies Needed for Small Industry

	No.
Adhesive bandages	100
Adhesive compresses	100
Adhesive tape	
0.5 in. by 10 yd.	1
1 in. by 10 yd.	1
1 in. by 2½ yd.	2
Analgesic (aspirin or similar)	100
Antiseptic	
2 oz. (physician's preference)	1
Applicators	100
Aromatic ammonia spirit (2 oz.)	1
Bandages	
1 in. by 10 yd.	4
2 in. by 10 yd.	6
3 in. by 10 yd.	2
Sodium bicarbonate (4 oz.)	1
Boric acid powder or ointment (4 oz.)	1
Buckle tourniquet	1
Castor oil or liquid petrolatum for eye injuries (2 oz.)	1
Cotton (0.5 oz.)	2
Cotton swabs	54
Magnesium sulfate (4 oz.)	1
Gauze bandage (1 yd.)	2
Measuring cup	1
Ointment for burns (1 oz.)	2
Paper tissues (boxes)	1
Paper cups	6
Scissors	1
Soft soap liniment (12 oz.)	1
Sterile absorbent gauze pads	
2 by 2 in.	24
3 by 3 in.	24
4 by 4 in.	24
Sterile eye droppers or 1 eyecup	2
Sterile eye pads	6
Triangular bandage	1
Tweezers	1
Wood splints	2
Wooden tongue depressors	12

CIRCUMORAL HYPERPIGMENTATION

TO THE EDITOR:—*A 40-year-old Chinese woman began showing areas of increased pigmentation circumorally and over the bony prominences. Blood pressure has remained normal, and the Kepler test shows normal results. Melanuria is present. Physical examination is negative, but the patient is very thin (94 lb. [42.6 kg.]—4 ft. 11 in. [149.9 cm.]), although her appetite is excellent. She has a temporomandibular arthritis that has responded to roentgen therapy. She has multiple vague complaints and is quite distressed by the cosmetic problems posed. A chronic otitis, which has responded to therapy and antibiotics, is present. Pelvic examination is negative. In the past four months the pigmentation has increased in density until now it is almost black over the bony prominences, with some discoloration of mucous membranes. Are there any further diagnostic studies or any type of therapy that would be of avail?*

Frank E. Glaser, M.D., Aiea, Oahu, Hawaii.

This inquiry was referred to two consultants, whose respective replies follow.—ED.

ANSWER.—Hyperpigmentation is usually attributed to physical or chemical agents, systemic abnormalities (particularly endocrine disorders), or cutaneous diseases. Circumoral hyperpigmentation occasionally occurs in patients who receive bismuth. It occurs, too, in erythrose peribuccale pigmentaire, a condition noted occasionally at the time of menopause in women with seborrheic skins. If a true melanuria exists, the presence somewhere of a melanoma should be suspected. If the pigment is due to homogentisic acid or alkaptonuria, one of the inborn errors of metabolism such as ochronosis must be considered. The Puetz-Jaeghers syndrome of mucous membrane pigmentation associated with intestinal polyposis, Hodgkin's disease, or other lymphoblastomas may also manifest peculiar types of pigmentary disorder.

ANSWER.—Circumoral pigmentation and pigmentation over the bony prominences is seen in many conditions such as malaria, leprosy, pellagra, hemochromatosis, lymphadenoma, abdominal carcinosis, ochronosis, colonic polyposis, Riehl's melanosis, melanoleukoderma, and fixed eruptions from drugs. This reply is limited in its scope to pigmentation due to abnormal production of melanin, as attention was focused on melanuria. From the brief description given of the lesions and the fact that a biopsy of the hyperpigmented areas was presumably not made, it is difficult to make a definite diagnosis; however, the following diagnoses must be considered: adrenal cortical hypofunction (Addison's disease), melanoderma (chloasma), leukoderma, and ochronosis. Hypoadrenocorticism in a milder (subclinical) state than the well-known textbook description of it is much more common than is generally supposed. The multiple vague complaints mentioned and the size of the patient, despite her excellent appetite, could possibly be due to hypoadrenocorticism. The following tests will aid in the diagnosis of a deficiency state of the adrenal cortex: (1) serum sodium and potassium, (2) blood sugar, and (3) nonprotein nitrogen; also, the use of adrenocortical hormone for a short period of time may influence the degree of hyperpigmentation and thereby aid in the diagnosis. While the hyperpigmentation of adrenal cortical hypofunction is usually more diffuse and generalized, it can be localized to areas of normally increased hyperpigmentation. Until a definite diagnosis is made, treatment with a diet high in sodium and low in potassium and adrenocortical hormone is suggested.

BLAND DIET AND ROUGHAGE IN COLITIS

TO THE EDITOR:—*Should cold cereals such as corn flakes, Wheaties, and puffed rice be considered in a roughage diet, or in a bland diet, as cooked cereals? I have a number of patients with duodenal ulcer and segmental colitis and am not certain whether they should be allowed cold cereals. Details on the roughage factor of cold versus cooked cereals would be helpful.* *M.D., New Jersey.*

ANSWER.—The cereals that are usually considered in a bland diet are cooked refined corn, rice, and wheat cereal; strained oatmeal; and commercially prepared cereals from corn or rice, free from outer coating, such as corn flakes and puffed rice (Mayo Clinic Committee on Dietetics: Mayo Clinic Diet Manual, ed. 2, Philadelphia, W. B. Saunders Company, 1954). The following table, which contains data from "Food Values of Portions Commonly Used" by Bowes and Church (ed. 8, Philadelphia, Anna de Planter Bowes, 1956), gives the amount of crude fiber in an average serving of some common cereals.

Amount of Crude Fiber in Cereals

Cold Cereals, 1 Cup	Crude Fiber, Gm.	Cooked Cereals, ¾ Cup	Crude Fiber, Gm.
Bran Flakes	1.3	Cream of Wheat	0.1
Cheerios	0.4	Malt-O-Meal	0.3
Corn Flakes	0.1	Oats, Rolled, or Oatmeal	0.4
Grape-Nuts (½ cup)	1.0	Pablum	0.3
Grape-Nuts Flakes	0.4	Ralston, Hot or Instant	0.5
Kix	0.2	Wheatena	0.5
Rice Krispies	0.1	Wheat Flakes	0.5
Rice, Puffed	0.2		
Wheat, Puffed	0.2		
Wheat, Shredded (1 large biscuit)	0.7		

TEST FOR BLOOD IN STOOL

TO THE EDITOR:—*What is an adequate office test for determination of blood in the stool?* *M.D., New York.*

ANSWER.—An ideal office test for determination of blood in stools should be a simple one, which will not give false reactions or a positive reaction if the patient is on a meat diet or is taking medication with iron. A test that fulfills these qualifications is the Ham's filter-paper method with benzidine dihydrochloride, as described by Hepler and others (Comparison of Tests for Occult Blood in Feces, *Am. J. Clin. Path.* **23:**1263 [Dec.] 1953), in which two solutions are required: one bottle having 1% benzidine dihydrochloride (1 gm. in 20 cc. of glacial acetic acid, 30 cc. of distilled water, and 50 cc. of alcohol) and another containing 3% hydrogen peroxide. The following technique is used: 1. With an applicator stick, a small portion of feces from the center of the specimen is taken, and a thin smear on filter paper covering an area 2 cm. in diameter is made. The filter paper should not be placed on a table top, or a substance on the table may give a false-positive reading. 2. Four drops of 1% benzidine dihydrochloride solution and four drops of hydrogen peroxide are added. The paper is then tilted to facilitate mixing. At the end of one minute a blue color diffusing from the feces should be noted. Any color in a ring that may occur at the edge of the solution on the filter paper should be disregarded, as the color should be over the fecal smear itself. The findings are read as follows: negative, no color one minute; 1+, faint blue in one minute; 2+, light blue in one minute; 3+, definite blue in one minute; and 4+, deep blue in one minute. A 1:100 dilution of blood in the feces will give a 3+ reading. Filter paper should be tested with the reagent to be certain that the paper alone will not give a false-positive test. A new solution should be made up every 30 days. The testing of the stool of a patient not on a meat-free diet is of value if the test is not too sensitive. In this respect, the Hematest tablets are unreliable as is the guaiac test. The simplicity of the Ham's filter paper method, the ease of reading the color reaction, and the stability of the reagent make this a good screening test.

BEHÇET'S SYNDROME

TO THE EDITOR:—*Where can a complement-fixation test on Behçet's syndrome (recurrent ulceration of the genitals, lesions of the mouth, and uveitis or iridocyclitis) be performed? I am under the impression that this disease is frequently overlooked.* *M.D., New York.*

ANSWER.—Complement-fixation tests are based on the antibody response to an infectious agent. Behçet's syndrome has not been proved to be an infectious disease, and complement-fixation tests, therefore, are not used as a diagnostic measure in this disorder. At present, the diagnosis of the disease is made on the basis of recurrent attacks of oral aphthae, genital ulcerations, uveitis and hypopyon, erythema nodosum, cutaneous ulcerations, arthritis, phlebitis, and central nervous system disturbances. Not all of these signs may be present in a given patient. The disease is resistant to all therapy. It has indeed been frequently overlooked, and this often seems to have been due to the fact that specialists tend to ignore recurrent signs in body areas remote from their own fields of interest. Recently Sezer (*Am. J. Ophth.* **41:**41-55 [Jan.] 1956) elaborated on the etiological role of a virus in this disease and the result of the complement fixation test of his patients in Turkey. These findings have not been confirmed to date.

PERTUSSIS AND MUMPS

TO THE EDITOR:—*Are there any therapeutic vaccines or serums of proved value for the treatment of pertussis or mumps? About 20 years ago several were advanced but were soon found to be of no value. Is there a company in the West that markets any such vaccine or serum? I would also like to have outlined the present accepted treatment for a moderately severe case of pertussis.* *M.D., New York.*

ANSWER.—For pertussis, human unconcentrated hyperimmune serum is of value but rarely available; however, a company in Berkeley, Calif., produces Hypertussis, a highly concentrated human hyperimmune serum. A company in Los Angeles also prepares a pertussis hyperimmune irradiated human serum that can be used for passive immunization or treatment. Hyperimmune gamma globulin has also been used. A company in Philadelphia makes a rabbit antipertussis serum. Human convalescent mumps serum has been used for treatment of mumps but is of doubtful value. Usually a child does not require any special medication. A company in Los Angeles also makes an irradiated human hyperimmune mumps serum that can be given intramuscularly or intravenously. For passive immunity, protection lasts usually from one to two weeks. Sometimes it seems to be of value when used for the treatment of severe mumps. For adult males diethylstilbestrol, 2 to 4 mg. orally daily for from four to five days, seems to be beneficial,

particularly if the patient has orchitis. The treatment required for pertussis will depend a great deal on the age of the patient. In the case of an infant there is probably nothing superior to an oxygen tent and good nursing care. (An aspirating machine may be helpful.) For an older child, it is important that he have outdoor fresh air or a well-ventilated room without exposing others to infection. If the paroxysms are severe, 2.5 cc. of Hypertussis intramuscularly once daily may be very helpful. Should the paroxysms be frequent, it may be advisable to have the patient take small quantities of food four or five times a day rather than three large meals. It is also a good plan to prescribe one of the tetracyclines as a prophylactic for secondary infections. In addition, a mild sedative will often have the effect of reducing the number of paroxysms. Neither the pertussis nor the mumps vaccine is used for treatment; they are for active immunization.

GRANULOMATOUS UVEITIS

TO THE EDITOR:—*What role do dental foci, such as apical abscesses, play in the etiology of a severe granulomatous uveitis?*

M.D., West Virginia.

ANSWER.—Generally, dental foci or any other focal infections are not considered to have an etiological role in granulomatous uveitis. Syphilis, tuberculosis, sarcoidosis, toxoplasmosis, brucellosis, sympathetic ophthalmia, fungi, and viruses are the usual causative agents. Nongranulomatous uveitis may in some patients be associated with a septic focus in the teeth, tonsils, nasal sinuses, genitourinary tracts, or intestinal tracts. The underlying fundamental cause in this type of inflammation is a bacterial allergy particularly due to streptococci. Irrespective of the possible role of focal infection in nongranulomatous inflammation, good hygiene requires the elimination of easily accessible conditions such as apical abscesses.

PHYSICAL FITNESS

TO THE EDITOR:—*Many articles have appeared in magazines and newspapers about physical fitness or the lack of it in the American male. I am puzzled as to what is meant by physical fitness. A man who can do 20 push-ups may not be physically fit to play a hard game of football. What series of exercises can I recommend to a middle-aged man to keep him physically fit, and at what point can I say that he is physically fit?*

M.D., Michigan.

ANSWER.—The basic criteria of physical fitness cannot be defined unless we ask, physical fitness for what? Objective criteria vary according to whether a person is (1) merely existing; (2) living a normal, happy, efficient life; (3) engaging in Olympic or lesser athletic competition; (4) undergoing varying stresses and demands of particular jobs; or (5) qualifying for the armed forces (even according to duties desired, the criteria are different, i. e., regular duties versus commando training or stress flying) in peacetime. Fitness is a "quality of life" based primarily on individual variables of heredity and environment and life habits. Positive physical fitness means the higher and highest degree of organic and muscular strength, endurance, agility, or special physical skill that an individual can attain through special, long-continued, gradually intensified activity or training. The techniques and methodology of such training are primarily the field of the physical director, the physical educator, and the coach or trainer—not the physician. The physician should be the guide as to the medical appropriateness of such activity at different times and stages. Definite accepted standards for such guidance are not as yet satisfactorily available. Varying clinical judgment is the guide at present. Setting-up exercises, walking, and moderate recreational sports and physical activities common to the home satisfy normal human needs. Regular programs of muscle-building and body-building and recreation common to Y. M. C. A.'s and athletic clubs satisfy somewhat higher fitness ambitions. Those adults who wish objective criteria for higher levels of fitness may find satisfaction in comparative results with either the Rogers or Cureton test standards. In aviation the Schneider index is commonly used, and other specialties use the more recent Carlson fatigue test. Either of the latter can be used as an office procedure. Many other tests are available, as noted by Schneider (Physiology of Muscular Activity, ed. 4, Philadelphia, W. B. Saunders Company, 1953) and Cureton (Physical Fitness of Champion Athletes, Urbana, Ill., University of Illinois Press, 1951). The need to reemphasize group and individual calisthenics and gymnastics in correlation with the present valuable educational and recreational competitive games played at school is essential in fighting against the inevitable tendency toward relative physical softness that has accompanied American prosperity and technological developments. Physicians can contribute much to the total picture in individual case guidance and patient education, as well as in community leadership, against the trend toward physical softness.

CHOLESTEROL IN VARIOUS FOODS

TO THE EDITOR:—*Could you send me a list of foods giving the amount of cholesterol and fat present in each for a given weight of each food? I have read the recent article on a similar subject by Lester M. Morrison, M.D., of Los Angeles and found it informative and interesting.*

J. C. Damitz, M.D., Akron, Ohio.

ANSWER.—The following table, taken from the book "Nutrition and Diet in Health and Disease" by McLester and Darby (ed. 6, New York, W. B. Saunders Company, 1952), gives the cholesterol content of some common foods:

Cholesterol Content of Foods *

Food	Total Cholesterol Mg./100 Gm. of Moist Food
Muscle meat	
Beef round (medium fat)	125
Beef round (lean)	95
Veal shank	140
Veal breast	100
Pork spareribs	105
Rabbit	50
Chicken (light)	90
Chicken (dark)	60
Duck	70
Pigeon	110
Variety meats	
Liver	
Lamb	610
Pork	420
Beef	320
Calf	300
Heart (beef)	145
Kidney (beef)	405
Sweetbreads	280
Tripe	150
Egg products	
Egg yolk	2,000
Fresh whole egg	468
Dairy products	
Fresh Jersey milk (3.7% fat)	24
Fresh Holstein milk (2.5% fat)	19
Butter	280
American cheese	160
Swiss cheese, processed	145
Cheese, Monterey Jack	190
Casein, raw	65
Fish and seafood †	
Oysters, eastern	230‡
Oysters, California	280–470‡
Crab	145‡
Tuna‡	149–172
Mackerel‡	240
Sardines‡	190
Codfish	50
Salmon	60
Shrimp	150
Turtle	70
Brewer's yeast, dry	680‡

* This table is based chiefly on the compilation by Okey, R.: Cholesterol Content of Foods, J. Am. Dietet. A. 21: 341, 1945; and personal communication from Dr. Okey.

† Total digitonin-precipitable sterol. These foods contain sterols other than cholesterol.

‡ Data from Geiger, E.: Substernal Pain, Queries and Minor Notes, J. A. M. A. 139: 194 (Jan. 15) 1949.

Dietary cholesterol occurs only in foods from animal sources; it is not present in plant foods. However, the body can synthesize cholesterol from either animal or vegetable fat, so the mere elimination from the diet of foods high in cholesterol does not necessarily result in a decrease in the blood cholesterol.

ALCOHOL IN THE BLOOD

TO THE EDITOR:—*Is there such a thing as a normal blood alcohol level? If so, does this reflect an abnormal metabolism, or would it be more prone to reflect the ingestion of alcohol in other things than intoxicating beverages, such as elixirs and vehicles?*

S. W. Scorse, M.D., Joplin, Mo.

ANSWER.—There is no normal blood alcohol level. Early investigators found reducing substances in the blood that were thought to be alcohol; however, methods more specific for alcohol fail to show this substance in the blood of normal individuals. A recently developed method for determining alcohol, in which alcohol dehydrogenase is used, is highly specific and

shows no normal alcohol. The alcohol that is occasionally found can be traced to the ingestion of substances containing alcohol, or the alcohol may be inhaled or may even be absorbed through the skin, as could occur from an alcohol rub.

DERMATITIS OF HANDS

To the Editor:—*For eight months a patient of mine who is a doctor has been taking 15 to 20 mg. daily of prednisone because of atopic eczema of the hands. When the dosage is reduced to 10 mg. daily, the condition becomes worse. Will this amount of medication over a period of time become harmful, and, if so, in what way? Tests for sensitivities have been negative. The chief dermatologist in a large clinic thought the condition was due to nerve tension associated with a busy surgical practice. He suggested a trip to Florida for two months, which the patient took, and the eczema cleared up while he was away.*

M.D., Kansas.

Answer.—Prednisone taken over a period of time may produce side-effects similar to those produced by older type steroids, particularly moon-shaped facies, increased supraclavicular fat deposition, acne, hirsutism, striae, gastrointestinal dysfunctions of various types, and a diabetogenic effect. Resistance to infection is reduced; there is increased tendency to hemorrhage; and osteoporosis may occur. It is unusual for atopic dermatitis to be limited to the hands. Dermatitis venenata is much more common, and the fact that the dermatitis disappeared while the patient was on vacation would suggest the latter diagnosis. The use of prednisone should be discontinued gradually, and by means of patch tests dermatitis venenata should be ruled out. Perhaps a so-called tranquilizing drug would be helpful.

ROUTINE BLOOD CELL COUNTS

To the Editor:—*At a hospital a new pathologist proposes to do hematocrit determinations only, instead of red blood cell counts and hemoglobin determinations on all admissions. Some members of the staff question this change in our routine. Some think that a red blood cell count is more valuable than a hematocrit determination. Please furnish information on the relative merits of these tests when used on a routine basis.*

M.D., Florida.

Answer.—It has become an increasing practice in many hospitals to determine the hemoglobin level, hematocrit, total white blood cell count, and differential count as the initial routine blood work. If there is any significant abnormality in the hemoglobin level, hematocrit, and/or the size, shape, and quality of the red blood cells as noted on the blood film when doing the white blood cell differential count, then a red blood cell count is done. If the hematocrit, hemoglobin level, and the appearance of the red blood cells are normal, then a total red blood count is probably of little value. Only under these circumstances is it believed that the red blood cell count can be validly eliminated as part of the initial "routine."

SURGERY AND POLYCYTHEMIA VERA

To the Editor:—*A 65-year-old man was found to have nonsymptomatic polycythemia vera prior to undergoing an elective cholecystectomy. The hemoglobin is 130%, and there are close to 8 million red blood cells. What complications might result from the polycythemia postoperatively? Should this condition be treated preoperatively, and, if so, what should be done?*

M.D., New York.

Answer.—Patients with polycythemia vera are prone to two postoperative complications: hemorrhage and thrombosis. The latter may be due to a marked increase in red blood cells and perhaps also to the dilated vessels that may persist even after the blood count has been brought to a normal level. There is no acceptable explanation for the hemorrhagic tendency. It is important not to operate on a patient with polycythemia vera unless it is necessary, and the patient should be prepared by a reduction of his red blood cell count. If this reduction must be attained rapidly, then phlebotomies are indicated. If time is not a factor, then radioactive phosphorus (P^{32}) may be used, but it takes at least three months to obtain results with P^{32}. Some hematologists use both P^{32} and phlebotomies at the same time. The hematocrit reading should not be above 50% before an operation is performed. Several factors have to be considered in this case, such as age, symptoms resulting from the gallbladder condition, and general condition. Whether the operation should be performed is a matter that the surgeon must consider, but under no condition should an operation be undertaken unless the count is brought down to normal, especially the hematocrit value.

SEVERE LOW BACK PAIN

To the Editor:—*A woman, 47 years old, has complained of severe low back pain radiating to the left thigh since 1949. The recurrent attacks last from three weeks to two months. At times there is no thigh radiation of the pain. She now has an attack associated with moderate sharp pain, generally down the left thigh. Her physical examination is negative, with the exception of hypesthesia on the anterior lateral leg and foot on the left side. There was found on x-ray examination a left-sided sacralization of the fifth lumbar vertebra, with mild left lumbar scoliosis, along with some sclerotic changes of arthritis in the lower part of the spine. She is slightly anemic, with a red blood cell count of 3,670,000 per cubic millimeter and a hemoglobin level of 10 gm. per 100 cc.; the white blood cell and differential counts were normal. No changes were noted in the urinalysis. Her Venereal Disease Research Laboratory test was negative. Might relief of symptoms be expected by removal of the left fifth lumbar process?*

M.D., Ohio.

Answer.—Lumbar transversectomy, because of a sacralized transverse process, was an operation that was carried out by some orthopedic surgeons about 30 years ago. The results from this operation were almost uniformly unsatisfactory. When a patient with a transitional lumbar vertebra begins to have back pain that radiates down into the thigh, there is always a possibility that a degenerated intervertebral disk may have protruded into the spinal canal. This should certainly be ruled out, either by myelogram before operation or by exploration at the time of surgery. Most of these patients, however, merely have an osteoarthritis in the abnormal joint, formed between the transverse process and the sacrum, or sacrum and ilium. If the patient cannot be made comfortable by the more conservative procedures of physiotherapy, with heat and massage and a chair-back type of brace, she is entitled to the benefits of surgery. The fifth lumbar intervertebral disk interspace should be examined. If there is a bulging disk, it should be removed. Regardless of whether there is a protruding disk, the operation of choice, which has given the highest degree of permanent relief of symptoms, has been arthrodesis of the fifth lumbar vertebral body to the sacrum.

CANCER OF COLON

To the Editor:—*What is the life expectancy for a 62-year-old man who was found to have an obstructing carcinoma of the splenic fixture of the colon, with metastasis to the liver? A resection was done removing the obstructed portion, followed by an end-to-end anastomosis. What treatment is recommended in such cases?*

M.D., Italy.

Answer.—Average life expectancy in a case of this sort is from 10 to 15 months. Death is usually due to inanition and cachexia because of massive liver involvement. Further treatment is symptomatic only.

MARRIAGE OF COUSINS

To the Editor:—*Probably it does not matter very much, but the individuals described in Queries and Minor Notes in* The Journal, *May 12, 1956, page 182, namely, the couple whose paternal grandfather and father, respectively, were brothers, were not second cousins as the letter states but first cousins once removed.*

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